

May 1948

VOLUME 1 NUMBER 1

Cancer

DIAGNOSIS
TREATMENT · RESEARCH



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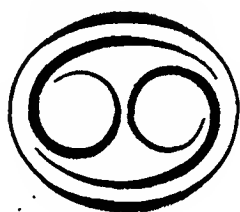
July 1948

VOLUME 1 NUMBER 2

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Cancer

A Journal of the American Cancer Society

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This First Issue of CANCER is Dedicated to the Memory of

JAMES EWING (1866-1943)

American Pioneer in the Field of Neoplastic Disease

Cancer

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CHRISTIAN ALBERT THEODOR BILLROTH (1829-1894)

BILLROTH joined Langenbeek's clinic as an assistant in 1854. In this brilliant circle he came into close contact with Meckel, von Hemsbach, von Bärensprung, von Graefe, and Wilms. He became a friend of Johannes Müller's son, and then of Müller himself. Stimulated by this great man, Billroth began to devote himself to pathological histology. His chief, Langenbeek, removed many tumors, and Billroth plunged into a microscopic study of this material. In 1855 the first fruit of this work appeared, a monograph on polyps. Billroth described and classified a series of these growths and emphasized that they did not ordinarily undergo carcinomatous degeneration.

This was the beginning of an absorbing interest in tumors which dominated a long surgical career. Billroth, it is fair to say, contributed more to the subject of tumors than any other surgeon who ever lived. To be sure, his career embraced the period in which the development of microscopic pathology and antiseptic surgery took place, making effective cancer surgery possible for the first time. Yet Billroth was among the first to master

these new techniques, and he accomplished more with them than any man of his time.

Although Billroth made important contributions concerning the surgical attack on most types of cancer, he is best known for having performed the first total laryngectomy (Ueber die erste durch Th. Billroth am Menschen, ausgeführte Kehlkopf-Exstirpation und die Anwendung eines künstlichen Kehlkopfes. Von Carl Gussenbauer: Arch. f. klin. Chir. 17:343, 1874), the first abdominal resection of a bladder tumor (Exstirpation eines Harnblasenmyoms nach vorausgehendem tiefen und hohen Blasenschnitt, Heilung. Von Carl Gussenbauer: Arch. f. klin. Chir. 18:411, 1875), and the first successful resection of the pylorus (Offenes Schreiben an Herrn Dr. L. Wittelshöfer. Von Prof. Th. Billroth: Wien. med. Wchnschr. 31:161, 1881).

It was Billroth's custom, both at Zürich and Vienna, to report *all* his surgical results each year. His *Chirurgische Klinik, Wien*, in which the treatment of a great number of cases of carcinoma was discussed, had a world-wide influence on cancer surgery.—

Cushman D. Haagensen, M.D.

SEPTEMBER, 1950

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GRANTS AND FELLOWSHIPS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is accepting applications for grants and fellowships. Applications for new grants will be received until October 1. Investigators now receiving grants will be notified individually regarding application for the extension of these grants. Final decision on grant applications will be made early in 1951. Grants approved at this time ordinarily will become effective July 1, 1951.

Fellowships available include both Fellowships in Cancer Research of the American Cancer Society and Damon Runyon Clinical Research Fellowships, financed by a grant from the Damon Runyon Memorial Fund to the American Cancer Society. Fellowship applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1, though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, Inc., on recommendation of the Committee on Growth, has awarded grants and fellowships approximating \$2,000,000. A program of similar magnitude is contemplated for the coming year.

Communications should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

GRANTS FOR ENVIRONMENTAL CANCER RESEARCH

The Committee on Growth of the National Research Council, adviser for research to the American Cancer Society, announces the formation of a Panel on Environmental Cancer with the following membership: Dr. Willard Machle, Chairman, Dr. Francis Heyroth, Dr. George H. Gehrman, Dr. Herman Lisco, and Dr. Norton Nelson.

Increasing realization of the importance of further research in environmental cancer led to the creation of this new panel that, at the outset, will concern itself with an evaluation of the status of knowledge in this field and with the formulation of criteria for the establishment of valid relationships between environment and occupation and the occurrence of cancer. The panel also will review applications for grants in support of research in these areas. These applications, as with others submitted to the Committee on Growth, will be received until 1 October.

Communications regarding grants may be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

Apologia

THAT cancer is attracting an ever increasing interest on the part of both the lay public and the profession is obvious. By popular appeals and by government appropriations, sums have been made available for the investigation and treatment of cancer that would have appeared unbelievably large a few years ago. It is unlikely that such funds will become less; they may well increase. The mere existence of adequate financial support stimulates research; and such research is now in progress in many laboratories. Governmental grants for the establishment of teaching faculties, professorships of oncology (preserve us from this word), will inevitably augment interest in cancer among clinicians in all categories. *Cancer has become a part of the activity of every practitioner of medicine.*

An outlet will then surely be required for the publication of this steadily increasing volume of work. It must be apparent to all authors who wait months or even more than a year for their manuscripts to be published by existing journals that, despite their efforts, the excellent journals now available seemingly have more material than they can publish within a reasonable period. Whereas medical journalism is certainly overcrowded, in that there are far too many journals of the variety essentially forced upon memberships of numerous medical societies, it is by no means replete in publications representative of truly scholarly endeavor.

Thus there is in America today no journal that accepts for publication papers dealing with all aspects of the cancer field: clinical, experimental and educational. These categories seem to have been separated since the decess of the very comprehensive American Journal of Cancer. Clinicians now read clinical journals; subvarieties of clinicians, their own special journals. Pathologists, chemists, physicists, biologists, statisticians, all read those publications that interest them and for

the most part know only a smattering, if anything at all, about what goes on in related fields. The experimentalist may not have enough general knowledge of cancer to know if his experiment has a logical basis. The clinician is apt to regard the pure experimentalist with disdain or distrust and to forget that, apart from mere techniques, almost all advances in the clinical field, especially in surgery, every extension of operability, every saving of life by means unknown a few decades ago, stem from the laboratory—either from the experimentalist or from the clinician with real breadth of view who has become an experimentalist temporarily. Surely therefore there is room for a publication that under a single cover will present the advances in cancer to readers with diverse interests.

It is not possible, however, for one journal to cover so large a subject as cancer in its entirety. Journals devoted almost exclusively to the publication of experimental cancer research already exist and it is not our desire to compete with these in general, therefore, we wish to afford a medium for the publication of work dealing with *human* cancer. We view this term "human cancer" in a very broad sense, including in it not only clinical work on any phase of human cancer, clinical investigation of human cancer, but also any experimental work which may be supposed to possess a relationship, albeit remote, to human cancer. To illustrate briefly: work in mitotic poisons conducted on lower animals would constitute acceptable material; similarly, papers on any phase of steroid physiology, cytochemistry, isotopes in metabolic studies, and the like. Papers dealing with straight organic synthesis should go elsewhere; so also, those concerned with animal genetics. It is difficult to describe any sharp line of demarcation. It would be better to envision a broad zone like the old Polish corridor trusting, however, that it will not engender quite so

much feeling on the part of the inhabitants of either side.

Many journals limit the length of papers they publish. It is not our intention to do so. Rather, we believe that if someone has something worth saying space should be provided in which to say it, assuming it is said with reasonable conciseness—is not padded with unessential material.

Certain papers make the life of an Editor difficult. Such, for example, are those from authors who deem it necessary to go back almost to Hippocrates in their quotations of "the literature." In this Editor's opinion much valuable space in journals is wasted in unnecessary reviews of past literature. He knows of no major discoveries and certainly of very few advances made through reading and especially through quoting all that has been said in the past. No originality is claimed for this viewpoint, since it appears to resemble that stated by Astley Cooper more than 100 years ago. This sort of "thesis" style should be discouraged and space saved for something more important. The occasional appropriate review article is, of course, in a different category.

Thought has been given to the inclusion of case reports. Certainly many case reports constitute mere repetition of well-known facts. Conversely, others are of distinct value: those dealing with really rare entities in the tumor field and those leading to a significant conclusion bearing upon some point in dispute. Hence such case reports will be welcomed.

Thought, too, has been given to papers involving the use of statistics, especially those concerned with "cure" of cancer. Medical statistics are great deceivers; they may mean much or little depending upon how they are obtained. A clinician reporting his cure rate after selection of those cases that he believes he has a chance of curing by virtue of the skill he may himself possess, or by those means of treatment in which he happens to be trained, is not presenting the true picture of the disease. He must present end results *for all cases presenting themselves to him irrespective of whether or not they may in the beginning appear curable*. Once having done so he may subdivide his material as he sees

fit. The common tendency to present cancer cure rates in glowing figures and in a sort of competitive spirit for the best five-year end results does not aid the patient with cancer.

We trust that adequate illustration can be furnished all authors. Authors should realize, however, that adequate illustration depends not only upon the willingness of the publisher to publish and on the quality of his reproduction but also, and to a much greater extent, upon the quality of the material submitted for publication. It is useless to submit poor photographs from poorly prepared subject matter and expect presentable results. An illustration must tell something to the reader and not merely mean something to the person who has seen the original material. Small size or, in photomicrographs, low magnifications are to be discouraged. Our finances do not permit us to provide illustration in color free of charge.

CANCER will include a section, *Current Cancer Literature*, comprising those titles in the current medical literature that deal with neoplastic diseases. It will endeavor to publish these promptly upon their appearance. Certain of these titles will be accompanied by abstracts. It is our intent to exercise selection in materials to be abstracted and not to abstract everything written on or remotely dealing with cancer. A survey would seem to indicate that perhaps 15 per cent of papers justify an abstract. Such books as properly belong in the cancer bibliography will be cited there with a descriptive abstract outlining the scope and purpose of the book, or, in revised editions, the scope of the revision.

The American Cancer Society has put its heart into the new journal. It has not stinted in its financial aid. All those physicians and investigators asked to aid as members of the Advisory Editorial Board have accepted and to these men go the thanks of both the Society and the Editor.

Finally, the Editor is the time-honored target for criticisms. Criticisms are welcomed since a positive response to intelligent constructive criticism may spell the difference between success and failure.

FRED W. STEWART, M.D.

SARCOMA ARISING IN IRRADIATED BONE

Report of Eleven Cases

WILLIAM G. CAHAN, M.D.,[†] HELEN Q. WOODARD, PH.D.,
NORMAN L. HIGINBOTHAM, M.D., FRED W. STEWART, M.D.,
and BRADLEY L. COLEY, M.D.

TWENTY years ago the trend toward the use of radium and roentgen rays in the treatment of all types of neoplastic diseases was approaching its peak. At that time, irradiation was used on benign and malignant tumors, either before or after operation, or both, or as the sole method of treatment.

With the passage of time and the accumulation of experience, our concept of the place held by irradiation in the treatment of neoplasms of bone has changed. At Memorial Hospital we have steadily inclined toward the belief that roentgen-ray or radium treatment is inadvisable for benign tumors of bone and for most associated bone conditions, particularly if the location of the lesion renders surgical treatment practical. Our reasons are:

1. Surgical measures yield more satisfactory results, afford an opportunity for microscopic study of the entire specimen, and avoid the risk of irradiating a malignant tumor under the mistaken impression that it is benign.

2. Many of these benign lesions are either radioresistant or only slightly radioresponsive.

3. In children, prior to epiphyseal closure, irradiation of lesions in the vicinity of growth centers may cause serious disturbances in bone growth with resultant shortening and even deformity.

4. An undesirable and extremely serious sequel of radiation therapy is courted: there is the possibility that, after an interval of years, bone sarcoma may develop at the site of the previous irradiation and a benign bone condition, with moderate incapacitation

as its most serious prognosis, may be converted into a rapidly fatal disease.

It is to this sequel that we wish to call attention here. We propose to summarize the literature dealing with both experimental and clinical production of bone sarcoma by irradiation; to describe eleven cases, personally observed, in which bone sarcoma developed at a period considerably subsequent to irradiation of benign bone tumors or of normal bone; to point out that when this sequel does occur, its presence is suggested by several clinically observable signs; and finally, to emphasize the hazard involved in the wide use of irradiation for nonmalignant lesions of bone.

EXPERIMENTAL PRODUCTION OF BONE SARCOMA BY IRRADIATION

Bone sarcomas have been produced experimentally by irradiation (see Table I). In four separate experiments, the bones of rabbits, rats, guinea pigs and fowl were given roentgen-ray irradiation; in nine others, radium and/or its emanation, radon, was administered by subperiosteal, intramedullary, or intravenous routes.

In the earlier experiments of Marie, Clu-net, and Raulot-Lapointe²⁴ and Lacassagne,^{21, 22} it was thought that chronic inflammation was a concomitant condition necessary for the production of sarcoma by irradiation. In line with the concept, a specific bacterium, *Streptococcus caviae*, was isolated and assumed to be essential to the production of bone sarcoma. Later, however, workers used irradiation alone effectively; and Dunlap et al. produced transplantable osteogenic sarcoma by feeding rats 100 μ gm. of radium.

Not all of the irradiated animals developed sarcoma, but in those that did, a relatively

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Received for publication, January 31, 1948.

TABLE I
EXPERIMENTAL PRODUCTION OF BONE SARCOMA

<i>Authors</i>	<i>Date</i>	<i>Animal</i>	<i>Dose</i>	<i>Other condition</i>	<i>Type of irradiation</i>	<i>Interval between last irradiation and sarcoma</i>	<i>Final Pathology Report</i>
Marie, Clunet, & Raulot-Lapointe	1910	rat	large; soft rays	irradiation-ulcer	x-rays	14 mos.	Polymorphous-cell sarcoma
Lacassagne & Vincent	1929	rabbit	1000 r	infection (<i>Streptococcus caviae</i>)	x-rays	6½ mos.	Osteogenic sarcoma
		rabbit	1980 r	infection	x-rays	36 mos.	Fibrosarcoma
Schürch & Uehlinger	1931	rabbit	1 µgm. sub-peritoneally	none	radium	18 mos.	Spindle-cell sarcoma with cartilage and osseous tissues
Sabin, Doan, & Forkner	1932	rabbit	5.1 µgm. intraven. (5 rabbits); 7.7 cc. of mesothorium (4 rabbits)	none	radium chloride mesothorium	11-19 mos.	Osteogenic sarcoma in 2 of 7 animals
Lacassagne	1933	rabbit	total of 1980 r	infection	x-rays	33 mos.	Periosteal spindle-cell sarcoma
Schürch & Uehlinger	1935	rabbit	vaseline gauze with 2.5 µgm.	none	radium or mesothorium	18-21 mos.	In 5 of 22 animals: 3 were osteoblastic and 2 were polymorphous- or spindle-cell sarcoma
Jentzer	1936	rabbit	none	none	radium	?	Osteogenic sarcoma
Ross	1936	rabbit	0.1 µgm.	none	radium element pack	?	Osteogenic sarcoma
Ludin	1937	rabbit	8000 r in 6½ mos.	none	x-rays	?	Chondrosarcoma
Dacis & Biltris	1931	guinea pig			radium, paraffin, diatomaceous earth	?	Osteogenic sarcoma
Hellner	1937	rabbit	2450 mg. hrs.	none	radium element pack (external application)	24 mos.	Polymorphous-cell sarcoma
Schürch & Uehlinger	1937	rabbit	0.0005 µgm.	none	mesothorium	21-29 mos.	Osteogenic sarcoma in 14 of 21 rabbits
Dacis & Biltris	1937	fowl	Collodion strips with radium sulfate	none	radium sulfate	4-5 yrs.	Osteogenic sarcoma in 2 birds
Dunlap, Aub, Evans Harris	1944	rat	feeding of 100 µgm.	none	radium	average of 12 mos.	Transplantable osteogenic sarcoma

long postexposure time interval—varying from six months to four to five years—elapsed before the tumor became evident. The histology of the subsequent lesions was varied and included fibrosarcoma, spindle-cell sarcoma, chondrosarcoma and, most frequently, osteogenic sarcoma.

BONE SARCOMA IN MAN DEVELOPING FOLLOWING IRRADIATION

The literature on clinical material includes the group of European patients with bone and joint tuberculosis who were treated by roentgen rays and subsequently developed sarcomas, Martland's now-famous collection of osteogenic sarcomas in radium-dial painters, and Hatcher's three cases.

The European group is usually listed as comprising eighteen cases. Actually, fourteen of these may be said to have been osseous, rather than soft-tissue, sarcomas, and it is with these that we are particularly concerned. Thirteen were diagnosed clinically as tuberculosis, which was histologically proved in only three; the fourteenth, as chronic arthritis. In thirteen instances, roentgen-ray therapy was used but the factors of therapy were not explicitly defined so that the tumor doses cannot now be estimated. The reports give the impression, however, that excessive amounts of irradiation were administered at frequent intervals and for a considerable period of time. The remaining case was treated by a combination of radium-emanation potions and radium-chloride injections for a very high total dose.

As was the case in the experimental animal tumors, an extended latent period intervened between the last roentgen-ray or radium treatment and the first clinical evidence of sarcoma: three to twelve years with an average interval of six and two-tenths years. The average age of the patients at the time the sarcoma appeared was 22.2 years, with the majority ranging between 11 and 25 years.

Histologically, the sarcomas proved to be various types of osteogenic sarcoma with a preponderance of cartilaginous elements in many. Cartilage appeared in all three of Hatcher's cases. In three patients of the Eu-

ropean series (Denks'. Marsch's, and Beck's fourth case) definite tubercles were present, but these were not in continuity with the sarcoma. Tubercles were not found in the final specimen in the remaining ten.

The diagnosis of tuberculosis in these cases was thought to suggest, along with the early experiments, that chronic inflammation was necessary to the development of irradiation bone sarcoma. Martland's ten cases of osteogenic sarcoma that ensued in radium-dial workers from seven to twelve years after exposure is evidence to the contrary. Of this group, there were eight osteogenic sarcomas—seven of medullary and one of periosteal origin. There were also an osteochondrosarcoma and a periosteal fibrosarcoma.

Hatcher has added three cases in only one of which was chronic inflammation a prominent feature, and, in that instance, it was the result of overirradiation rather than a primary condition. One of his patients (see Table 2) had a chondroblastoma of the tibia which received an approximate tumor dose of 7000 to 8000 r. but the osteogenic sarcoma that followed six years after the roentgen-ray therapy was in the fibula within the field of irradiation; the original tibial lesion remained sclerosed. His second case was initially a histologically proved benign giant-cell tumor of the radius that was irradiated with an unknown quantity of radium and roentgen rays, sufficient, however, to cause skin ulceration and infection and atrophic, exfoliative dermatitis overlying the involved bone. The tumor of the radius was subsequently resected, but a fibrosarcoma developed eleven years later in the portion of the ulna that lay within the path of the therapeutic beam. In his third case, a primary chondrosarcoma developed in a presumably normal rib that lay within the field of roentgen-ray therapy used twelve years previously subsequent to a radical mastectomy.

Jaffe¹⁵ reports a lesion of the humerus "almost certainly a bone cyst [that] was misdiagnosed as a giant-cell tumor and given a course of irradiation therapy, with baleful consequences. In this case, six years after the radiation treatment, a fibrosarcoma developed in the radiated lesion."

TABLE 2
COLLECTED CLINICAL CASES OF BONE SARCOMA FOLLOWING RADIUM OR ROENTGEN-RAY THERAPY
(Exclusive of Martland's Ten Cases)

Case	Author	Year	Location	Treated primarily for	Age at onset of sarcoma	Sex	Agent used	Interval between irradiation and ensuing sarcoma (years)	Histologic type of sarcoma reported
1	Beck	1922	Wrist; lower 1/3 radius	Tuberculosis (clin. diag.)	39	F	X-rays	6	Pleomorphic spindle-cell with osseous areas
2	Beck	1922	Knee; lower 1/3 femur and upper tibia	Tuberculosis (clin. diag.)	20	M	X-rays	3	Pleomorphic spindle-cell with osseous and cartilaginous areas
3	Beck	1922	Knee joint	Tuberculosis (clin. diag.)	15	M	X-rays	4	Pleomorphic-cell with cartilaginous areas
4	Marsch	1922	Knee joint; lower femur tibia, fib.	Tuberculosis (clin. diag.)	12	M	X-rays	6	"Mixed cell." Tubercle was found
5	Marsch	1922	Knee joint; lower femur	Tuberculosis (clin. diag.)	17	M	X-rays	8	Ossified "enchondroma with lung metastases"
6	Beck	1924	Knee joint; lower femur	Tuberculosis (clin. diag.)	11	F	X-rays	6	Pleomorphic spindle-cell sarcoma with bone and cartilage; tubercles not in continuity with tumor
7	Baumann	1927	Elbow; distal humerus	Tuberculosis (clin. diag.)	23	F	"General doses"	6	Pleomorphic-cell
8	Jaruslawsky	1929	Knee joint; femur	Tuberculosis (clin. diag.)	15	M	X-rays	8	Giant-cell sarcoma
9	Küttner	1931	Knee joint; femur	Tuberculosis (clin. diag.)	11	F	X-rays	3	Pleomorphic spindle-cell
10	Denks	1931	Knee joint	Tuberculosis (clin. diag.)	12	F	X-rays	7	Osteochondromyxosarcoma. Tubercle
11	Gruca	1934	Knee joint; femur	Tuberculosis (clin. diag.)	16	F	X-rays	5	Pleomorphic-cell with cartilaginous areas
12	Becker	1936	Knee joint; femur, patella	Tuberculosis (clin. diag.)	25	F	X-rays	10	"Primitive" chondrofibro-ostoid

TABLE 2 (Continued)

13	Hellner	1937	Metacarpal	Tuberculosis	40	M	X-rays	8	Pleomorphic-cell
14	Nørgaard	1939	Tibia	Chronic arthritis	56		Radium locally; emanation "potions"; RaCl ₂ injections	8	Spindle-cell fibrosarcoma
15	Hatcher	1945	Tibia	Chondroblastoma of tibia	23	M	X-rays	4	Chondrosarcoma of <i>fibula</i> (note that original lesion was <i>tibia</i> ; latter, did not show tumor 4 years later).
16	Hatcher	1945	Wrist	Benign giant-cell tumor	29	F	X-rays and radium	11	Fibrosarcoma with areas of tumor cartilage in <i>ulna</i> . (note that original giant-cell tumor was in <i>radius</i>)
17	Hatcher	1945	7th rib	Postoperative irradiation carcinoma of rt. breast	49	F	X-rays	12	Chondrosarcoma of 7th rib

In another communication, Jaffe, Lichtenstein and Portis, in discussing the therapy of giant-cell tumors of bone that are accessible to surgery argue against the use of radiotherapy by noting that "there has been an apparent increase in the number of aggressive and malignant metastasizing giant cell tumors since the era of radiation therapy began. It is possible, of course, that such reports reflect simply a keener interest in the subject, but the burden of proof lies on those who support the use of irradiation, since the earlier writers have generally stated that death of patients with giant cell tumor eventually resulted from hemorrhage or infection rather than malignancy. Furthermore, our files include the records of two patients in each of whom malignant transformation of a giant cell tumor and pulmonary metastasis developed a number of years after ostensible improvement or 'cure' following radiation therapy. Altogether, the foregoing observations are not intended to imply that carefully controlled therapeutic irradiation of a giant cell tumor is necessarily hazardous in all instances, but they are disturbing enough to suggest that the problem requires renewed consideration." We are in complete accord with this conclusion.

The literature concerned with the "spontaneous" malignant change of a benign bone lesion contains several cases that might be examples of irradiation-produced sarcomas. Indeed, several authors in this group suggest this possible cause-effect relationship. Thus Kilgore, in discussing his hesitancy in using roentgen-ray therapy in a progressively malignant lesion in a 37-year-old woman who had refused surgery, states that "modern 'deep therapy' is still relatively new and we probably do not yet know the whole story of its undesirable effects on non-malignant tissue." He quotes as object lesson the foregoing sarcomas that have been reported as developing in joint tuberculosis.

Although the case that Kilgore reports certainly progressed from a benign to a malignant tumor without irradiation, the history is that of a lesion that seemed to have possessed progressive tendencies from its clinically determinable inception. In his article,

however, there is mentioned a case of Francisco, Pusitz, and Gerundo.

A 9-month-old child had a "soap bubble" central lesion below the upper epiphysis of the tibia, that was regarded as a bone cyst and was given roentgen-ray therapy for a year, factors unknown. Extensive calcification of the lesion was observed five years later and she was regarded as cured. At 9 years of age, pain returned to the area of the original lesion after a local trauma, a chondrosarcoma was found, and the limb amputated. The authors interpreted the early lesion as a bone cyst, but no microscopic report of its benign nature was available.

Kilgore thought that it might have been a cartilaginous rest, but the irradiation, the latent period of nine years, and the malignant change are certainly to be noted for possible interrelationship.

Piqué and Schajowicz report two cases:

In 1931, a 41-year-old woman injured her knee and a roentgenogram showed a tumor involving the internal condyle of the femur which was treated for the next year with interrupted doses of roentgen rays, factors unknown. Two years later, she came to the hospital from which the report stems, and an operation yielded a thick grayish membrane lining a cystlike cavity, but no specimen was analyzed histologically at that time; a tibial transplant was inserted. A roentgenogram in 1938 showed increased density in the zone of the operation. At the end of that year she developed pain in the area which rapidly changed from intermittent to continuous and eventually became unbearable. A rapidly growing mass appeared at the site.

Because amputation was refused, an aspiration biopsy was performed. This showed a fibroblastic sarcoma with many atypical cells and many typical and atypical mitoses. She received further roentgen-ray treatment and died six months later of pulmonary metastases.

The authors comment that a lag period occurred eight years after the onset of the tumor and seven years after irradiation, and that the gross anatomical form of the original lesion suggested a giant-cell tumor—most certainly a nonmalignant lesion.

The second case occurred in a 19-year-old girl who fell and hit the medial surface of her tibia in December, 1938. A tumor was

noticed the next day; one week later a roentgenogram was taken and a curettage performed, followed by forty roentgen-ray treatments. Pain returned in three months at which time a necrosis of the superior one-third of the tibia was observed in the roentgenogram as well as an ulceration overlying this area and the popliteal space. The skin showed irradiation changes that extended to the bone in one place. This area finally epithelialized but in December, 1944, intense pain returned and there was roentgenographic evidence of a fracture of the femur and osteolytic changes in both tibia and femur. The original biopsy, made six years previously, was reviewed and proved to be that of a benign giant-cell tumor, Jaffe's grading I to II. An amputation was performed. The tumor mass was found to involve both the upper tibia and the lower femur.

Microscopically, giant cells were no longer present but instead there was a typical fibroblastic sarcoma made up of fusiform cells presenting atypical changes and atypical mitoses, with an abundance of collagen.

The authors did not believe that this case was initiated by roentgen-ray therapy, for they had a similar case that had gone eight years without sarcomatous degeneration. As will be seen later, twenty-two years elapsed between irradiation and the development of sarcoma in one of our cases of benign giant-cell tumor.

Brunschwig reports a series of nine cases of giant-cell tumors of bone in which irradiation—or curettage followed by irradiation—had been used from three and one-half to twelve years previously. These were followed carefully in order to observe the changes, either microscopic or roentgenographic, that occurred at the tumor site.

One (Case IX) was in a 20-year-old woman who had a "scraping" in 1921 for a lesion of the radius the size of a hen's egg; in the next two years this was followed by numerous roentgen treatments and radium applications, but it is impossible to obtain information as to the dosage. A draining sinus developed that, on re-exploration by curettage, yielded tissue diagnosed as giant-cell sarcoma. Because of the draining sinus and erosion of the distal radius, a sequestrectomy was performed in 1928 and, in 1929, an osteotomy of the lower end of ulna, to correct hand position. No further sinuses ensued. In 1934, eleven years after her previous roentgen-ray therapy,

a tender swelling developed over the lower end of the ulna and a multilocular, expanding cystic lesion was found on the outer aspect "away from the surface that was adjacent to the affected (but since removed) radius." A graft was inserted; and in 1937, the patient was apparently without evidence of recurrence.

The histological report showed the tumor to be an expanding highly osteolytic lesion composed of spindle cells varying in size, shape, and arrangement and exhibiting numerous mitotic figures. Throughout the section were numerous small giant cells of the foreign body type and true tumor (of the stroma) giant cells. In some areas there was "tumor osteoid" tissue. Diagnosis was osteogenic sarcoma of bone or giant-cell tumor undergoing malignant change.

He comments that "two factors must be considered in etiology of the second neoplasms: first, trauma, and, second, the apparent intensive roentgen and radium irradiation received to the area several years earlier."

In Simmons' series of end results in the treatment of giant-cell tumors taken from the Bone Sarcoma Registry files, Case 295 had a lesion of the upper end of the femur the initial biopsy of which showed a "typical giant cell tumor." Remarkable improvement followed an unquoted amount of high-voltage roentgen-ray treatment and the patient was considered cured. Six years later, deformity of the hip and nodules of the overlying skin appeared and a biopsy, substantiated by a later autopsy, showed "highly malignant osteogenic sarcoma."

In all of these cases, there is one feature which seems to preclude the possibility that they originally represented instances of malignant giant-cell tumor or osteogenic sarcoma associated with many giant cells: namely, the long latent period of five or more years before malignant change became evident. It is unlikely that a malignant tumor would have remained dormant for so long or that it would have been controlled by roentgen-ray therapy, only to reappear in a different histologic form years later.

SELECTION OF MATERIAL

The cases that follow were selected to fulfill certain prerequisites:

1. There must have been microscopic or

roentgenographic evidence of the nonmalignant nature of the initial bone condition.

2. Irradiation must have been given and the sarcoma that subsequently developed must have arisen in the area included within the radiotherapeutic beam.

3. A relatively long, asymptomatic latent period must have elapsed after irradiation before the clinical appearance of the bone sarcoma. In these cases, this has been longer than the so-called five-year-cure period.

4. All sarcomas must have been proved histologically.

The clinical material falls into three general divisions: (a) five cases in which there is histological evidence of the benign nature of the primary bone lesion; (b) four cases in which there is roentgenographic evidence of an initially benign bone lesion; (c) two cases in which roentgen-ray therapy was used for overlying soft-tissue lesions, following which osteogenic sarcoma developed in normal bones within the field of irradiation.

CLINICAL OBSERVATIONS

(See Table 3)

Family and Past History. With the exception of cases 10 and 11, these were non-contributory.

Age. The ages listed in Table 3 are those at the time of the diagnosis of the sarcoma and range from 9 to 59 years. The average age was 34 years with most of the cases occurring between 21 and 35 years. Oddly enough, the youngest and oldest patients belong in the third group, i.e., those in whom sarcoma developed within normal bones.

The relative youthfulness of the group is consistent with that reported in the literature. The European cases occurred at an average age of 22.2 years and two of Hatcher's three cases were in 22- and 23-year-old individuals.

Sex. There are seven males and four females in the series.

Bone Involved. The humerus and the femur were each involved three times, the tibia, ethmoid, mandible, maxilla and rib, once.

Initial Lesion. In Group I, those with a histologically proved benign primary lesion, there were two giant-cell tumors—one proved

TABLE 3
ANALYSIS OF AUTHORS' ELEVEN CASES

No.	Initials	Age (at time of sarcoma) and sex	Bone involved	Primary condition & diag. basis	Physical agent & dose	Estimated tumor dose	Interval between last irradiation and sarcoma	Final diagnosis	End result
1	W.S.	23 M	Mandible	Ossifying fibroma; microscopic	200 kv x-rays Jan. '38-Mar. '38 2500 r 1939 1000 r X 2 ports	4500 r	7 yrs. from 1st 6 yrs. from 2d	Osteogenic and/or fibrosarcoma	Living with disease, Nov., 1947
2	I.H.	59 M	Femur	Benign giant-cell tumor; microscopic	185 kv x-rays Jan. '25-Aug. '25 1480 r med. 1760 r ant.	Antero-medial surface of bone had about 3500 r; post-lat. had 1750 r	22 yrs.	Osteogenic sarcoma; giant-cell tumor seems replaced by fibrous tissue	Died with disease Jan., 1948
3	F.B.	35 M	Humerus	Benign giant-cell tumor; microscopic	200 kv Apr. '36-May '36 1440 r X 3 ports	3070 r	10 yrs.	Osteogenic sarcoma merging with residual giant-cell tumor	Died; pulmonary metastases, May, 1947
4	J.B.	23 M	Humerus	Bone cyst; microscopic	130 kv x-rays Jan. '22-May '22 2750 r X 3 ports. 200 kv x-rays July '22-Dec. '22 1100 r X 2 ports 550 r X 1 port.	Between 6000 & 9000 r	13 yrs.	Medullary spindle-cell osteogenic sarcoma	Alive and well March, 1947
5	G.B.	42 M	Femur	Osteoid osteoma; x-rays	200 kv x-rays Oct. '31-Feb. '32 2800 r X 3 ports	5730 r	9 yrs.	Osteogenic sarcoma with sclerosing tendencies	Died; metastases to many bones, Feb., 1947
6	I.W.	24 M	Femur	Bone cyst; x-rays	175 kv x-rays Oct. '29-Mar. '30 1200 r ant. port; 1800 r post. port.	1550 r	17 yrs.	Chondrosarcoma. No evidence of giant-cell-tumor	Died; pulmonary metastases, Feb., 1946
7	M.J.N.	22 F	Tibia	Fibrous dysplasia; x-rays	Rad. emanation pack. Apr. '19 19,827 mc. hrs. at 10 cm.	Approx. dose, ant. margin of tibia 1510 r	8 yrs.	Osteogenic sarcoma	Died; pulmonary metastases, June, 1929

TABLE 3 (Continued)

8	B.M.	21 M	Humerus	Bone cyst; x-rays	140 kv x-rays Feb. '33-June '33 2250 r; 200 kv x-rays Jan. '34-Oct. '37 3500 r	5580 r in 4 yrs.	9 yrs.	Osteochondro- sarcoma; fairly low grade	Regional recurrence, twice. Died Jan. 8, 1948, multiple metastases
9	R.W.	26 F	Maxilla	Cloudiness of maxillary antrum	200 kv x-rays Apr. '30-Dec. '31 3370 r	3600 r	13 yrs.	Ostcogenic sarcoma	Alive 3½ yrs. after radical surgery
10	K.P.	55 F	2d rib	Post-op. radical mastectomy	200 kv x-rays Sept. '35- Sept. '36 2200 r X 3 ports	Dose to site of fracture in 2d rib 4480 r	11 yrs.	Ostcogenic sarcoma	Living with disease, Oct., 1947
11	E.B.	9 F	Ethmoid	Retino- blastoma	200 kv x-rays June-Oct. '39 9000 r X 2 ports; Mar.-Apr. '41 2400 r X 4 ports	16,000 r in '39; 9,000 r in '41	7 yrs. from '39; 6 yrs. from '41	Ostcogenic sarcoma	Died, July, 1946 extensive local recurrence

by open biopsy and one by aspiration biopsy; one case each of a bone cyst and an ossifying fibroma; and one in which early biopsy failed to show tumor cells.

In Group II, the diagnosis by roentgeno-gram alone can be only presumptive. Yet, by assembling all available clinical data such as the history, position and roentgenographic appearance of the lesion and age of the patient, a reasonably accurate diagnosis can be made. If, in addition, one considers that from eight to seventeen years elapsed after roentgen-ray therapy before sarcomas developed, it seems justifiable to consider these initial lesions benign. In this group, then, there were two bone cysts, one fibrous dysplasia, and one osteoid osteoma.

In Group III, there was roentgenographic evidence of underlying normal bone in both cases prior to irradiation.

Type of Therapy. In ten cases, roentgen-ray treatment was used with filters ranging from 0.5 mm. Cu to 1. mm. Cu plus 1.25 mm. Al filter. In the eleventh case, a radium emanation pack was employed. The individual dosages ranged from 100 to 200 r X 3 to 800 r to one port daily. Intervals of treatment ranged from daily through twice weekly and twice monthly. The initial dose of the radium emanation pack was 19,286 mc. hrs. at 10 cm.

Tumor Dose. Tissue-dose calculations for roentgen-ray treatments were made by the tables in "Physical Foundations of Radiology";¹⁰ those for gamma-ray treatments, from the calibrations made at Memorial Hospital for the equipment used. Whenever possible, the depth of the bone below the surface was determined by measurements on roentgenograms. When suitable ones were not available, measurements were made on another person of approximately the same size and age as the patient. The calculations were made for the point at which the sarcoma apparently originated, or, if this was not clear, for the region in the affected bone that received the largest dose. There is considerable uncertainty about the exact factors used in roentgen-ray treatments given prior to 1930. Therefore, estimates of depth doses for patients treated before that date can be consid-

ered as indicating only the order of magnitude of the exposures received.

All of the depth-dose tables used in the present calculations were obtained by measurements made in material equivalent to soft tissue in absorption and scattering characteristics. It has long been known that the absorption of roentgen rays by bone exceeded that by soft tissue. Recently, Stenstrom has shown that the ionization produced in bone by roentgen rays of 100 kv. to 140 kv. is nearly four times that produced in soft tissue under the same conditions. The difference diminishes with increasing voltage, so that it is only a few per cent for 1000 kv. roentgen rays and gamma rays. Despite the excellence of Stenstrom's treatment of the problem not enough data are available at present to permit correction of depth-dose calculations made by means of standard tables for the greater ionization produced in bone. The figures given here indicate the magnitude of the doses when computations are made by conventional methods. It must be understood that the actual energy absorbed in the bones of patients treated at the lower voltages was considerably larger than the figures would indicate.

In a previous paper, it was found⁴¹ that bone doses greater than 3000 r usually caused permanent damage to the regenerative capacity of normal bone. Doses greater than 5000 r are likely to cause complete devitalization of adult bone, but the bones of children survive much higher doses. All the patients in the present series except case 6 (I.W.) and case 7 (M.J.N.) received doses that would be expected to cause moderate to profound depression of the metabolic activity of bone. This suggests that the development of osteogenic sarcoma in irradiated bone is analogous to the development of leukemia in marrow or epithelioma in skin that has undergone severe atrophy from irradiation.

Latent Period. The latent period was calculated from the date of the last roentgen-ray or radium treatment prior to the onset of the clinically determinable sarcomatous change. It ranged from five to twenty-two years and averaged eleven and two-tenths years.

In four instances, roentgen-ray therapy was repeated once, one and three years after the first series; otherwise, treatment was given in one continuous course, which in some patients extended over periods up to one year.

Symptoms of Malignant Change. In all nine cases in which a primarily benign lesion was treated, the most prominent symptom of malignant change was the rather sudden onset of steady and progressively increasing severe pain in the area. The intensity of this pain readily distinguished it subjectively from the vague aches and pains that had been present in the intervening years. In one of these pain occurred only at night. In reviewing the cases reported in the literature, pain has been a consistent finding.

Swelling in the area with or without dysfunction was the second most consistent symptom.

In the two cases in which normal bones changed character, there was no pain, but swelling and edema of the overlying structures were prominent symptoms.

Certainly malignant change should be suspected and the possibility of its presence investigated before further irradiation is administered, if a patient suddenly develops pain in the area of a previously known benign lesion that has remained asymptomatic for a period of five or more years after fairly extensive irradiation.

Final Diagnosis. All eleven cases in this series have a final histological diagnosis.

Osteogenic sarcomas were present in nine. In one of the two cases in which giant-cell tumor was the initial diagnosis, the sarcoma was seen to be adjacent to a fibrosed area, presumably old giant-cell tumor. In the other, the osteogenic sarcoma could be seen to merge with residual giant-cell tumor but was nevertheless a new and distinct entity.

The remaining lesions that developed osteogenic sarcoma were a microscopically proved bone cyst, an ossifying fibroma of the mandible, a roentgenographically diagnosed osteoid osteoma, a chronic productive osteitis, a fibrous dysplasia, a normal rib, and a normal ethmoid.

Chondrosarcomas developed in two cases of bone cyst (roentgenographic diagnosis).

Prognosis. Seven patients have died of disease; one, of causes probably related to disease. One patient is alive and well as of March 1947; this patient had a microscopically proved bone cyst of the humerus, devel-

week, for a total of 2500 r. The factors were 200 kv., 0.5 mm. Cu filter, 50 cm. TSD. Treatment was completed March 23, 1938.

One year later, because there was no regression of the swelling, he was given 1000 r to each of two 6 × 8 cm. portals overlying

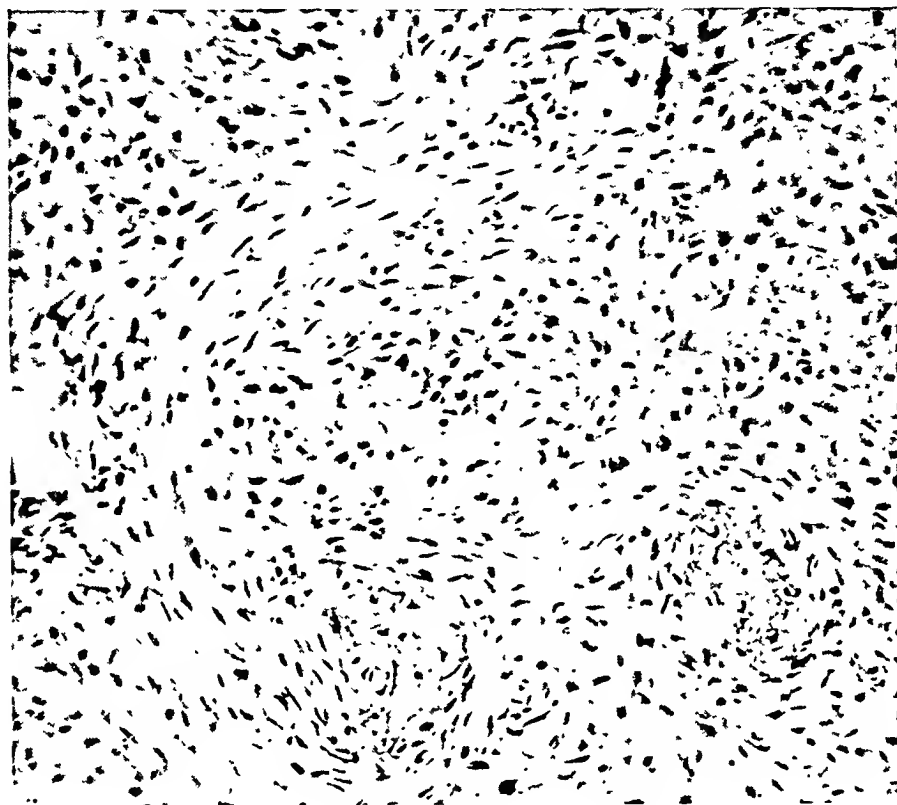


FIG. 1. *Case 1. Ossifying fibroma of the mandible.*

oped a medullary osteogenic sarcoma thirteen years later, and had an interscapulothoracic amputation twelve years ago. Another patient is alive four years after excision of a sarcoma of the maxilla.

Two patients with sarcoma are alive and their outlook is hopeless.

CASE REPORTS

Group I. Microscopic Proof of the Benign Character of the Original Bone Lesion.

Case 1. W. S., male; 23 years old when sarcoma developed. Admitted to Memorial Hospital, August 30, 1946.

In 1938, eight years before admission, roentgen-ray therapy was given to a swelling of the left jaw at another hospital: This consisted of ten treatments, 150 r each, through a 10 × 10 cm. portal, given three times a

the left mandible. The factors of irradiation were 200 kv., 1.0 mm. Cu plus 1.25 mm. Al filter at 50 cm. TSD. The tumor dose from the irradiation in 1938 and 1939 was in the neighborhood of 4500 r. A biopsy had been made just prior to this course of therapy (Fig. 1) which was interpreted as an ossifying fibroma.

Although the swelling persisted, the patient was asymptomatic until July, 1945, six years after the last course of irradiation, when pain returned to the left jaw and an unerupted wisdom tooth was extracted because it was considered the cause of this difficulty. He had a purulent discharge both from the tooth socket and from a fistulous tract that developed externally. The following month, he underwent a partial mandibular resection and was told postoperatively that he had an osteogenic sarcoma. For three weeks he was improved, but thereafter the pain and swelling returned more aggressively than before.

He was treated from December 4, 1945 to January 12, 1946, with 2500 r to one field 8×15 cm. directly over the mandible and 2450 r to each of two 6×8 cm. submaxillary and lateral cervical fields. From June 13

part of the pterygoid process and styloid process of the temporal bone; a Padgett graft was placed in the defect. Local recurrences were excised in January and February, 1947 and all of these specimens were found to

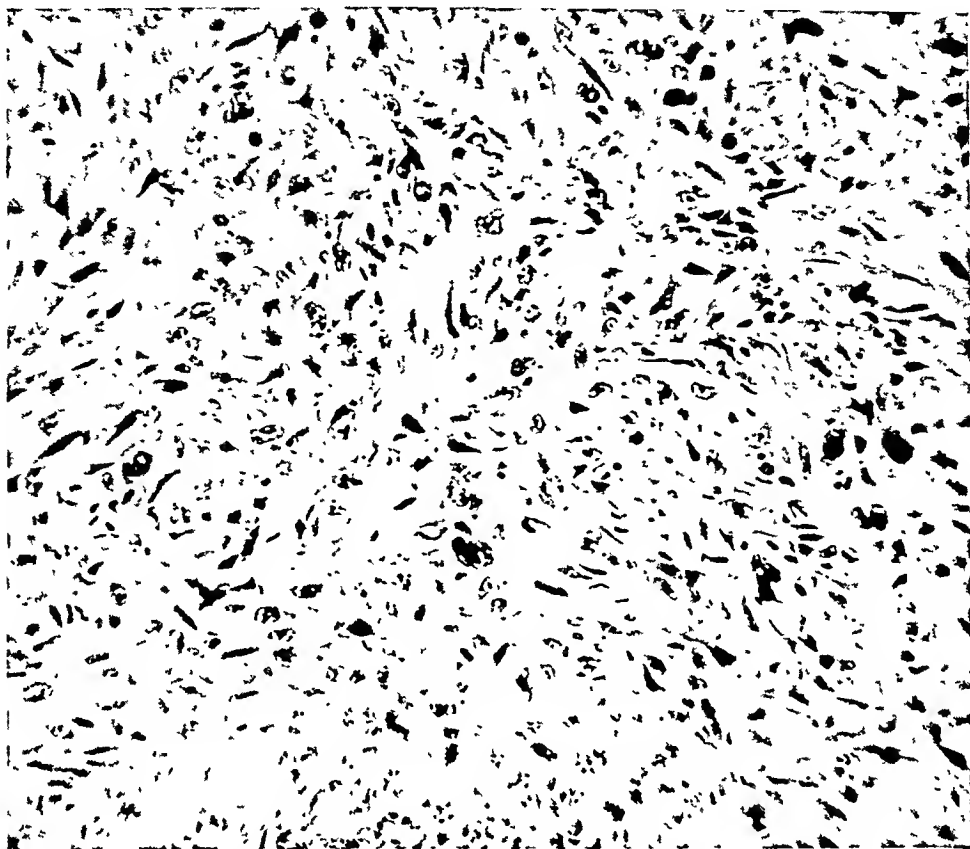


FIG. 2. *Case 1. Osteogenic sarcoma arising six years after irradiation of the lesion shown in Fig. 1.*

to June 26, 1946, he received 1000 r to each of two circular fields, 7 cm. in diameter, at the angle of the left mandible. In all cases, the factors of treatment were as before.

He was finally told there was nothing more to be done and he sought treatment at Memorial Hospital.

Physical examination showed complete paralysis of the mandibular ramus of the seventh nerve on the left and a moderate degree of trismus. A 5×5 cm. sloughing, foul crater with indented ulcerated edges extended into the mouth. This lay at the former site of the angle of the left jaw. The surrounding tissue was erythematous for 3 to 4 cm. Introrally, most of the ulceration lay in the posterior third of the alveolar ridge with extension into the gingivobuccal gutter.

On September 11, 1946, after ligation of the external carotid artery and tracheostomy, a left mandibulectomy was performed with excision of the posterior and lateral maxilla,

be osteogenic sarcoma (Fig. 2).

In November, 1947, a note was made that the disease was then progressing rapidly, and that the dura had become involved.

Interval between the last irradiation and sarcoma formation (i.e., exclusive of roentgen-ray therapy administered after the sarcoma had developed): six years.

Case 2. I.H., male; 59 years old when sarcoma developed. Admitted to Memorial Hospital, January 12, 1925.

The patient was admitted in January, 1925, with a history of pain after repeated injuries to his left knee as a result of falls three years previously. At first the pain was relieved by physiotherapy, but a year before admission it became persistent in spite of this treatment. A biopsy and curettage was then performed at another hospital in 1923, following which he wore a splint for fifteen

months. The specimen was reviewed at this hospital and showed: "... a giant cell tumor of bone. The giant cells are limited to an inner zone, are rather numerous in this zone, many are of very large size as in the typical benign type. The section, however, shows a zone of very cellular tissue 12 mm. thick, composed of very few giant cells of small size and very many closely packed small *hyperchromatic spindle cells*. The section as a whole indicates a tumor of *considerable growth capacity*, capable of recurring locally."

The patient was referred here for roentgen-ray therapy and received treatments from January to August, 1925, to each of two portals: the medial and anterior lower femur: 480 r, 200 r, 640 r, 640 r, 640 r, and 640 r. The factors were 190 kv., 0.5 mm. Cu and 1 mm. Al filter, 50 cm. TSD. It has been impossible to calculate the tumor dose accurately after twenty-two years because of the method of recording then used, but the anteromedial surface of the lower end of the femur in the region of the tumor received about 3500 r and the posterolateral margin about 1750 r. The patient remained essentially asymptomatic except for marked limitation of motion of the knee joint.

He was readmitted to Memorial Hospital on July 28, 1947, because the occasional intermittent pain, experienced during the intervening years, had become increasingly severe and steady in the previous month, requiring the use of a cane and narcotics.

Physical examination revealed a well-healed scar on the medial aspect of the knee, induration, drying, fibrosis, and telangiectasia of the skin overlying the medial condyle. The medial condyle was absent, on palpation. There was a slight varus deformity of the knee. Flexion was limited to about 100° by pain. A roentgenogram at this time showed an irregular osteolytic area along the upper portion of the medial aspect of a tumor that occupied the medial condyle of the left femur.

An aspiration biopsy was performed (Fig. 3) and a report of osteogenic sarcoma made. The patient was adamant in refusing amputation. In November, 1947, an open biopsy was performed. The sections revealed an osteogenic sarcoma just above a calcified fibrosed area that occupied the region from which the original lesion had been removed surgically. Sections of this latter area showed calcified fibrous tissue that seemed to fill out the region left by removal of the benign giant-cell tumor; there were no signs of recurrence of this tumor. Again, the patient re-

fused amputation and died January 11, 1948. No autopsy was performed and the cause of death was not clear.

Interval between last irradiation and sarcoma formation: twenty-two years.

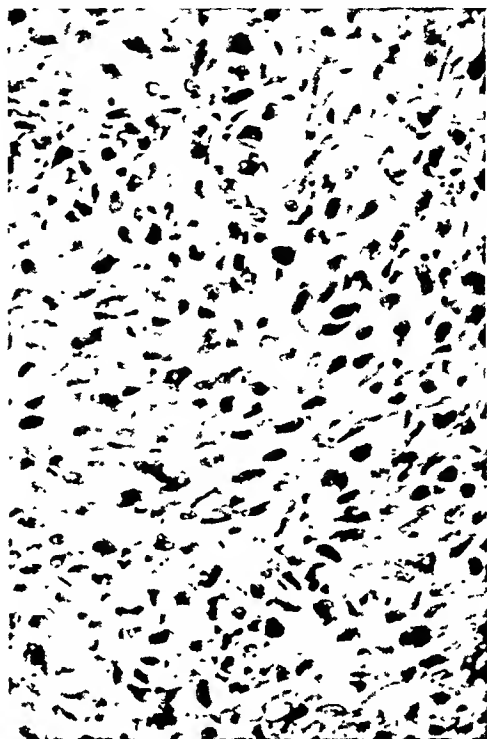


FIG. 3. Case 2. Osteogenic sarcoma developing twenty-two years after irradiation of giant-cell tumor.

Case 3. F. B., male; 35 years old when sarcoma developed. Admitted to Memorial Hospital June 17, 1936.

In October, 1934, the patient turned over on a motorcycle, landed on his right shoulder, and sustained a fracture about 4 cm. below the head of the humerus. At another hospital, the arm was strapped in place for seven weeks; thereafter it was gradually returned to use although it never seemed to regain its full strength.

One and a half years later, the patient sustained another fracture of the right shoulder from a minimal trauma. After roentgenographic examination, the arm was immobilized with adhesive strapping and infra-red treatments were given. Finally resort was had to roentgen-ray therapy when roentgenograms showed what was described as a "giant cell tumor of the head and upper portion of the shaft of the right humerus."

Between April 21 and May 27, 1936, the patient received eight roentgen-ray treatments to each of three portals (superior, an-

terior, and posterior) measuring 10×15 cm. The factors were 200 kv., 0.5 mm. Cu and 2 mm. Al filter, 40 cm. TSD. This totaled 1440 r, measured in air, to each of the three portals. It was estimated that the prox-



FIG. 4. Case 3. Giant-cell tumor of the upper humerus prior to irradiation.

imal margin of the tumor received 3070 r, the distal margin, 2480 r.

Ten days following his last treatment, on June 17, 1936, he was admitted to Memorial Hospital. Physical examination showed the skin over the entire right shoulder to be tanned and desquamating, but no actual blistering was observed. Pressure over the head of the humerus caused considerable pain. The patient was able to raise his arm, but experienced pain when it was abducted beyond 90° . Some enlargement was noted about the right shoulder.

A roentgenogram (Fig. 4) dated June 17, 1936, was reported: "giant cell tumor, upper end of right humerus, apparently growing rather rapidly."

An aspiration biopsy performed at this time showed benign giant-cell tumor. (Fig. 5). He was placed in a modified Velpeau dressing, immobilizing the entire shoulder with arm abducted at 90° and flexed at the elbow at 90° .

A roentgenogram made November 10, 1937 (Fig. 6), showed dense ossification of the upper portion of the shaft of the humerus; physical examination revealed about 50 per cent of normal shoulder function.

The patient stayed away from the follow-up clinic for seven years.

He was readmitted to Memorial Hospital

on December 17, 1946, with a history of having noted pain in upper arm and shoulder for two weeks, increasing limitation of motion, and increase in bulk. Three days before admission a soft, tender swelling had been noted anteriorly on the upper arm.

Examination of the upper arm revealed a firm, central tumor mass that was slightly tender.

An aspiration biopsy was performed and the pathologist reported "believe this will turn out to be malignant giant-cell tumor. Nuclei getting atypical, and in the clot no giant cells are seen."

A roentgenogram on December 17, 1946 (Fig 7), showed "cortical destruction present for about 3 inches of the upper portion of the shaft of the humerus with the formation of a soft tissue mass and very slight periosteal change. There has been decalcification in the region of the old giant-cell tumor. The lesion is in intimate association with the acromion process."

On December 23, 1946, an interseapulothoracic amputation of the right upper extremity was performed. The significant portion of the pathologic report is as follows: Gross: "the point of interest is at the upper end of the humerus where the anatomical head has been largely replaced by extensive tumor growth, measuring 6×7 cm. It is worthy of note that the overlying skin in this area is said to have been treated by irradiation at an earlier period in the patient's history but does not show scarring or telangiectasia, or any evidence of irradiation changes at this time. The joint capsule appears to have been ruptured at one point, but it is not clear whether this was due to tumor or associated inflammatory and perichondritic changes. The tumor extends out into the soft tissue and has invaded the deltoid muscle until a shell of the latter muscle, approximately 2 cm. thick, is all that remains, bulging laterally and covering the tumor mass. There are numerous soft fleshy nodes in the axilla, none over 1.5 cm. in diameter, and all appearing uninvolved by the tumor process. There is a small pathologic fracture tangentially through the articulating surface of the humerus, but there is no complete transverse fracture producing preternatural motion."

Microscopic (Fig. 8): "There are small residual foci that retain the structure of giant-cell tumor which does not look malignant. However, these areas merge with fully malignant osteogenic sarcoma which is highly cellular and pleomorphic and which here and there produces small foci of atypical bone and cartilage. This is not the expected

evolution of a giant-cell tumor which becomes malignant and, although there is no proof, it suggests that this is a radiation osteogenic sarcoma."

On March 5, 1947, a chest roentgenogram was negative and there was no other evi-

The initial diagnosis in case 2 was proved by open biopsy and in case 3, by aspiration biopsy. Dr. Dallas B. Phemister concludes his description of the pathologic findings in case 2 with: "It seems to me that the long inter-

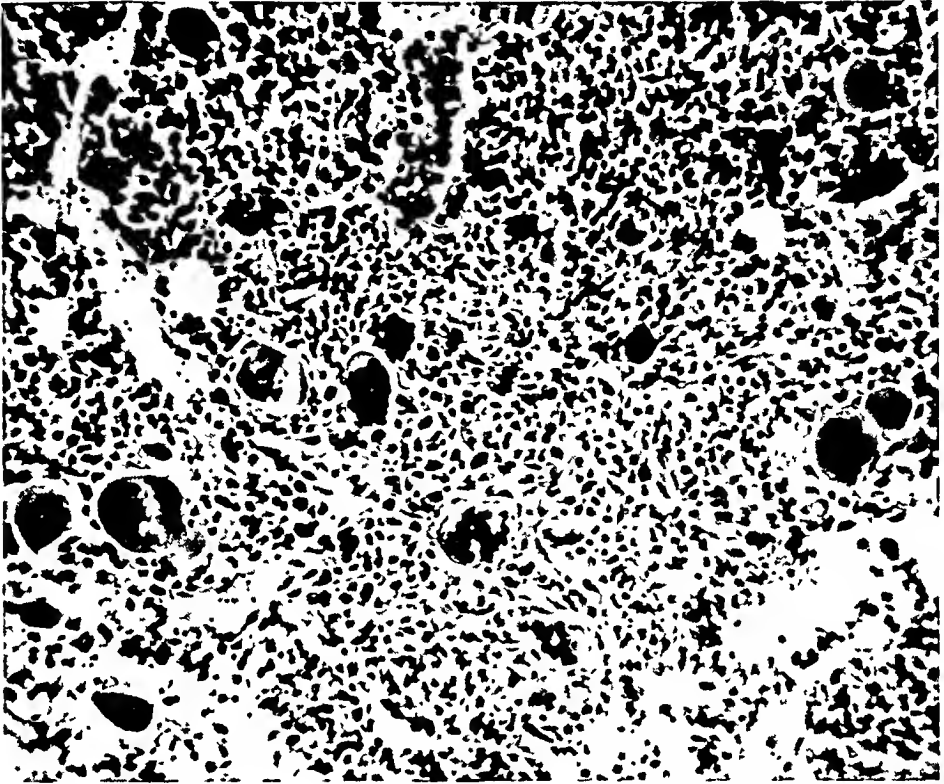


FIG 5. Case 3. Microscopic appearance of the lesion shown in Fig. 4.

dence of disease. However, by May 15, 1947, there were extensive pulmonary metastases, and the patient died ten days later.

Interval between roentgen-ray therapy and sarcoma formation: ten years.

Cases 2 and 3 are examples of initially benign giant-cell tumors diagnosed microscopically (although slides are no longer available). These two cases are distinguishable from the giant-cell tumor that becomes malignant spontaneously in ways other than by mere histological difference; thus, the clinical history of the malignant giant-cell tumor is that of progressive and rapid growth which is little influenced by irradiation and/or curettage for more than a few months at a time. Its usual course progresses to malignant change within a three-year period from the onset of symptoms.

val between the removal of the giant cell tumor and the development of the sarcoma justifies the diagnosis of sarcoma produced by irradiation."

The pathologist commented on case 3 that: "The residual focus of giant-cell tumor in this final specimen does not look malignant." This makes it probable that the sarcoma of the humerus did not evolve out of the previous benign giant-cell tumor.

Case 4. J. B., male: 23 years old when sarcoma developed. Admitted to Memorial Hospital March 18, 1935.

Fourteen years prior to his admission, when the patient was 9 years of age, he had a fist fight with some other boys and was struck on the right shoulder but developed no subsequent pain, swelling, or incapacity.

About one year later, at the age of 10 years, while he was ice skating, he fell backwards as his feet slid forward, and the force

of the fall was received on both elbows, principally the right. Pain in the right arm followed immediately and, although there was no external evidence of injury, it gradually became stiff. After two weeks of persistent



FIG. 6. *Case 3. Roentgenographic appearance following irradiation.*

pain and difficulty in putting on and removing his coat, he saw his family doctor who made roentgenograms of the right arm. The patient's father was told that he had a bone sarcoma and immediate amputation was advised. This was refused and he was taken to another hospital where roentgen-ray therapy was given as follows: From January 18 to May 23, 1922, to three portals (probably anterior, posterior, and lateral), in doses of 550 r (in air), he received a total of 2750 r \times 3. The factors were 130 kv., 0.5 mm. Cu filter (TSD and Ma. not mentioned).

On July 11, September 25, and December 12, 1922, an additional 1100 r was given to two portals and 550 r to the third portal. The factors were: 200 kv., 0.75 mm. Cu filter (TSD and Ma. and portal size not mentioned).

It was estimated that this patient received a final bone dose between 6000 and 9000 r.

It was stated that, following the above therapy, the stiffness increased so that the treatments were abandoned. He went to another, very reliable hospital and on January 18, 1923, had a curettage of a "bone cyst of the proximal end of the humerus in the region of the epiphyseal line." (No roentgenogram is available.)

"Gross Pathological Description: Curetting consists of spicules of bone, partly organized blood clots, bits of cartilage and strips of thin, smooth, white shining membrane resembling synovial membrane. All of the cu-



FIG. 7. *Case 3. Appearance ten years after irradiation.*

rettings were examined under the hand lens and identified as above. The appearance of the tissue did not suggest new growth.

"Microscopic Appearance: Several pieces of curetted material, differing somewhat in appearance but representative of all of the curettings, were sectioned. Some show partly organized blood clot, others show a chronic inflammatory tissue. Some of it is old, dense, fibrous tissue, some is quite recent, soft, cellular and containing many new capillaries and granulation tissue. There is no evidence of neoplasia." Section received from that hospital, March 24, 1947, was diagnosed as bone cyst at the Memorial Hospital.

Following this curettage, the arm was placed in traction; one week later, a spontaneous fracture occurred at the site of the lesion and the patient was told that the arm would never heal. He received massage during the subsequent twelve months and developed a flail joint at the site of fracture, with deformity and very limited function.

For the next ten years he went without treatment. In June, 1934, while helping a friend move furniture, he felt a sharp pain over the anterior surface of the right shoulder. He did not consult a physician but maintained the arm in constant rest.

In August, 1934, he was seen at Memorial Hospital for the first time, but no evidence of tumor was observed and he was referred to an orthopedic hospital where no therapy was

administered. In March, 1935, he was referred back to Memorial Hospital because it was felt that he now had a tumor that had become malignant. He had lost 38 pounds in the six-months' interval.

tase—5.6 units; phosphorus—4.23 mg. per 100 cc.; calcium—11.0 mg. per 100 cc.

On March 25, 1935, a right interscapulothoracic amputation was performed. The specimen was reported as "medullary spindle-

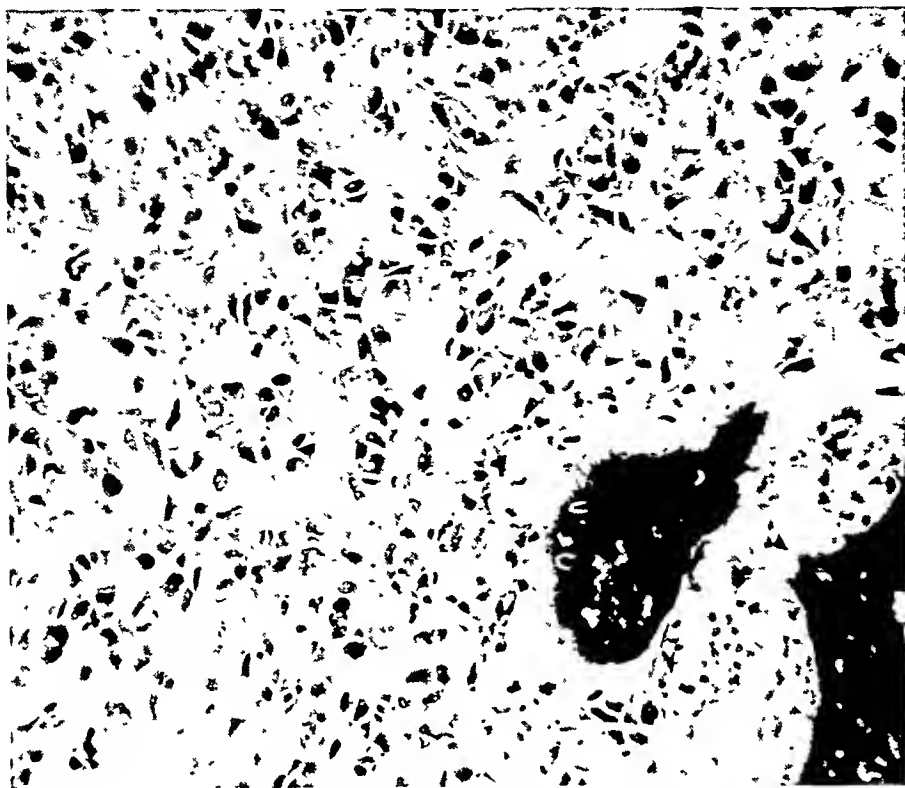


FIG. 8. Case 3. Osteogenic sarcoma; microphotograph of lesions shown in Fig. 7.

The patient appeared emaciated and pale. There was marked shortening of the right arm which measured 23 cm. in length, whereas the left arm was 38 cm. long. An 8 × 10 cm. bulge was present over the anterior portion of the right shoulder joint and extended over the pectoralis major. Just over the head of the humerus there was a 2 × 1 cm. localized swelling that was fluctuant and inflamed. No motion could be elicited about the shoulder, but false motion was present below the joint. The overlying skin for an area 18 cm. in length was roughened, thickened, and telangiectatic, presumably from previous irradiation.

A roentgenogram on admission, March 18, (Fig. 9), showed: "The remaining portion of the humeral head has been largely destroyed along with the upper one-half of the shaft." An aspiration biopsy was diagnosed as "spindle-cell sarcoma—probably one of medullary spindle-cell osteogenic type." Blood chemistry at this time was: phosphatase—5.6 units; phosphorus—4.23 mg. per 100 cc.; calcium—11.0 mg. per 100 cc.

cell osteogenic sarcoma. Nodes free."

The patient was given twenty-five injections of Coley's toxin subsequent to this. His alkaline phosphatase increased to 14.0 units and the phosphorus to 5.11 mg. two weeks after operation but returned to normal a month later and have remained so ever since.

On February 26, 1947, he was seen in follow-up and no evidence of disease was demonstrable.

Interval between last irradiation and sarcoma formation: thirteen years.

Case 5. G. B., male; 42 years old when sarcoma developed. Admitted to Memorial Hospital February 12, 1932.

The patient was first seen at Memorial Hospital in February, 1932, at the age of 32 years. He complained of pain about the medial surface of the right knee of eighteen months' duration; this had become steadily worse, particularly at night, and was associ-

ated with swelling and progressive incapacitation for the previous eight months.

A year before this admission (October 21 to 26, 1931), he had received a total of 800 r (measured in air) of high-voltage roentgen-



FIG. 9. Case 4. Roentgenogram of the humerus, thirteen years following roentgen-ray therapy for a bone cyst of the upper humerus. Osteogenic sarcoma present at this time.

rays to each of three portals over the anterior and both medial and lateral sides of the right knee, 200 r to each of three fields a day. A second series was given in December, 1931, at another hospital: 1200 r to an anterior and 1000 r to a lateral port at the rate of 100 r to two fields daily. The tumor dose at 1 cm. below the anterior margin of the femur was approximately 3850 r, although calculations are uncertain because of the lack of information about the factors of irradiation for first series. The factors assumed were 200 kv., 0.5 mm. Cu filter, 100 cm. square field, 50 cm. TSD.

At a second hospital, an open biopsy was made of the diffusely dense and sclerotic area at the lower third of the right femur. The operative note mentions that there was a small amount of "pus" noticed at operation, but no other comments were made. The pathology report on this specimen was "rarefied bone with fatty marrow; no tumor at all in these sections."

He was then admitted to Memorial Hospital for further roentgen-ray therapy. A roentgenogram at that time showed that the operative biopsy specimen had been taken from within the area of increased density. (Fig. 10) Physical examination revealed the right knee held fixed in 170° extension. A scar from a recent operation was present along the lateral surface. There was no tenderness to palpation. Circumferential measurements at the upper margin of the patella was 42 cm. compared with 37.5 cm. on the left side; 5 cm. above the patella margin: Right, 42.5 cm. and left, 38.1 cm.; 10 cm. above the patella margin: Right 44.4 cm. and left, 32.2 cm.

At that time, two diagnoses were entertained: osteitis following an old Brodie's abscess or sclerosing osteogenic sarcoma.

From February 12 to 17, 1932, the patient received 800 r \times 3, the portals measuring 12×6 , 12×8 , 12×6 cm. each to the lateral, medial and anterior aspects of the lower right femur; factors: 198 kv., 30 Ma., 0.5 mm. Cu filter, 50 cm. TSD.

A roentgenogram taken two months later: "previous described area of decreased density shows evidence of filling in, and the entire bone appears more dense than before."

Symptomatically, he improved from the day after the biopsy at the previous hospital and remained symptom-free for nine years. Follow-up roentgenograms in 1938, 1939, and 1940 showed no change in the appearance of the tumor.

In November, 1941, he was readmitted with a history of increasing pain in the right knee in the previously treated area, which grew steadily and rapidly worse over a three-to four-week period. Physical examination showed tanning of the overlying skin and a tender, indurated knee joint with enlargement of the lower end of the femur at its medial border. A pathological fracture was suspected (see Fig. 11). The previous operative scar was noted.

An open biopsy was performed, and followed immediately by a mid thigh amputation. The pathologist's report was "osteogenic sarcoma with sclerosing tendencies."

For six months, he progressed well and then, in May, 1946, extensive pulmonary metastases were observed. Accordingly, he received 2000 r \times 4 to each right and left anterior and posterior chest portals, measuring 16×12 , 15×18.5 , 20.5×12.5 , 21×13 cm. The factors were 250 kv., 30 Ma., 1.5 mm. Cu filter, 70 cm. TSD, in daily dosages of 400 r.

From October to December, 1946, he received nitrogen-mustard injections intraven-

ously without demonstrable benefit. A roentgenogram showed metastases in the lower lumbar spine and pelvis. He died in February, 1947.

The interval between the last irradiation

Case 6. I. W., male; 24 years old when sarcoma developed. Admitted to Memorial Hospital October 16, 1929.

When the patient was 8½ years old his parents noticed that he limped. After two



FIG. 10. *Case 5. Roentgenogram of the lesion regarded as osteoid osteoma or sclerosing osteitis.*

and sarcoma formation was nine years.

In a sense, this case belongs in both clinical groups, I and II, for the biopsy in the area of density at the lower end of the femur (see Fig. 10) showed no tumor cells, and the roentgenographic appearance is not specific but suggestive of a benign tumor such as an osteoid osteoma. Support for this diagnosis is afforded by the history of relief of the bone pain following the "unroofing" of the involved area, although no specific osteoid tissue could be found on reviewing the sections. The escape, at operation, of a small amount of pus which showed no growth on culture, and the diffuse, dense roentgenographic appearance also suggests a chronic non-specific inflammatory condition of bone.

Group II. Roentgenographic Evidence of the Presumably Benign Character of the Original Bone Lesions



FIG. 11. *Case 5. Osteogenic sarcoma arising in the lesion shown in Fig. 10, nine years after irradiation.*

months without improvement, roentgenograms were taken elsewhere and the patient was referred to Memorial Hospital on October 16, 1929. The physical examination was negative. On the day of admission, stereoscopic roentgenograms of the right hip revealed evidence of a process involving the neck of the femur, apparently medullary in origin. (Fig. 12.) This may be considered, at present, to have been a bone cyst or a fibrous dysplasia.

Roentgen-ray therapy was begun in October, 1929, when the right femur received 600 r to anterior and posterior 4 × 4 cm. portals. Two months later he received an additional 600 r to a posterior 4 × 4 cm. portal. In March, 1930, he had 590 r each to anterior and posterior femoral portals measuring 8 × 6 cm. and 6 × 4 cm. respectively. The factors in all instances were 175 kv., 0.5 mm. Cu filter, 50 cm. TSD.

The dose to the center of the tumor is now estimated to have been 1550 r.

A roentgenogram (not now available) made in April, 1930, was described as showing "further improvement (calcification?) when compared with previous film."

From March, 1930, until September, 1944,

ability was even more marked.

He was admitted to Memorial Hospital on June 20, 1946. A roentgenogram (Fig. 13) showed areas about the right hip that were considered to be suspicious of malignant tu-



FIG. 12. (Left) Case 6. Bone cyst of the upper femur.

FIG. 13. (Right) Case 6. Osteogenic sarcoma developing in the same lesion, seventeen years after irradiation.

he was asymptomatic. He joined the armed forces in 1943 and served two years in the infantry. In September, 1944, he began to notice stiffness of the entire right leg each morning on arising, but marching relieved it; a few weeks later pain and stiffness appeared in the right hip, accompanied by difficulty in walking. A diagnosis of neuritis was made and bed rest advised. At one Army hospital a roentgenogram was diagnosed "fibrocystic disease of the right femur." At another hospital a curettage was proposed, but instead he was given 1800 r to each of two 8×15 cm. portals, anterior and posterior, directed to the upper femur. The factors were 200 kv., 15 Ma., Thoraeus filter, 50 cm. TSD. This treatment was administered between April 23 and May 15, 1945.

There was temporary relief of pain, but this returned in a few months and his dis-

mor. The serum phosphatase, calcium, and phosphorus were normal.

On September 6, 1945, a specimen of bone was obtained from the femur which was reported as "low grade chondrosarcoma." A chest roentgenogram showed numerous round opacities typical of metastases. The patient died in February, 1946.

Interval between last irradiation and sarcoma formation: seventeen years.

The appearance of the primary lesion (Fig. 12), when the patient was $8\frac{1}{2}$ years old, is strongly suggestive of bone cyst, although an enchondroma could conceivably simulate this picture. It seems unlikely that, had the symptoms been produced by an enchondroma, a small tumor dose of 1550 r would have sufficed to control them for seventeen years. Al-

dredge, in his collection of 152 cases of solitary fibrocystic disease of bone, found that of 33 treated with irradiation either alone or combined with surgery, two developed sarcomatous changes; there were no examples of malignant degeneration in the 119 cases treated without irradiation.

Case 7. M. J. N., female; 22 years old when sarcoma developed. Admitted to Memorial Hospital April 18, 1919.

The patient was first admitted at the age of 13 years with a history of sudden pain in the right shin associated with a slight swelling six years previously. She remained without symptoms until two weeks before admission when she had an attack of severe pain in this leg and the swelling increased and persisted. On physical examination the upper third of the right tibia had a 9×5 cm. swelling which was not tender on deep palpation; the overlying surface was somewhat pigmented. A roentgenogram at that time showed that the upper third of the right tibia contained a cystlike formation which obliterated the medullary cavity and that destruction of the cortex over the anterior surface of the bone had occurred but was limited by the periosteum. She was treated by radium emanation pack with a total of 19,827 mc. hrs. in two doses over a 70 cm. square area at 10 cm. distance, on April 17 and 23. The tumor dose to the anterior margin of the tibia was 1480 r and to the posterior margin, 730 r.

Subsequent to this, there was roentgenographic evidence of some sclerosis throughout the cavity. The patient continued to have pain which seemed to be relieved for at least four months, coincidental with the administration of iodides and mercury intramuscularly.

The patient was examined routinely each year and remained asymptomatic until August, 1927, when a definite increase in the prominence of the tibia was noted, and a roentgenogram showed some suspicious densities in the surrounding soft tissue. A right mid thigh amputation was performed in February, 1928. The pathological findings were: "Osteogenic sarcoma, large polyhedral cells, cartilage, osteoid tissue, and callus production with much necrosis."

The patient developed metastases in the lungs, clavicle, and groin, and died in June, 1929.

Interval between last irradiation and sarcoma formation: nine years.

The original roentgenographic diagnosis of this case was bone cyst but, in the light of our present knowledge, the lesion was more probably a monostotic fibrous dysplasia. The final specimen was an osteogenic sarcoma

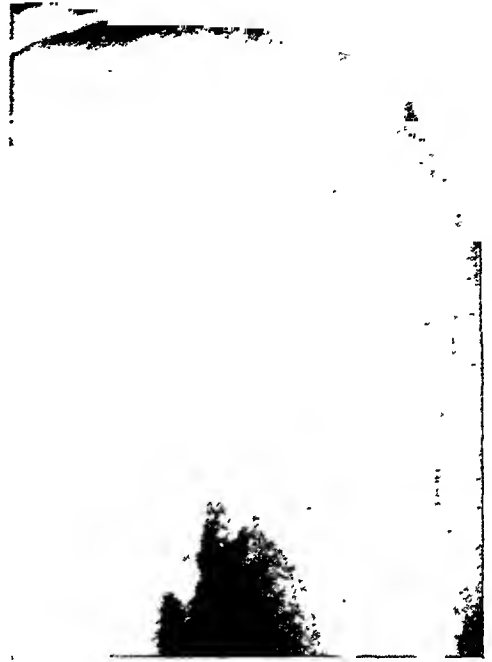


FIG. 14. *Case 8. Bone cyst of the upper humerus in a boy of eight years.*

with telangiectatic areas, Grade III.

It is unlikely that we are dealing with a spontaneous development of osteogenic sarcoma in fibrous dysplasia since the sarcomas we ourselves have reported in such circumstances have not formed cartilage or osteoid tissue.

Case 8. B. M., male; 21 years old when sarcoma developed. Admitted to Memorial Hospital September 7, 1946.

In 1933, thirteen years before his admission to Memorial Hospital, the patient fell and fractured the upper portion of the left humerus. Roentgenograms showed a rarefied area at the fracture site (Fig. 14), which was considered a simple bone cyst although an enchondroma or nonosteogenic fibroma were also mentioned as possibilities.

Roentgen Therapy: From February to June, 1933, he was given five treatments of 450 r each: two to anterior portals, two to posterior portals, and one to a lateral portal. The factors were 140 kv., 4 Ma., 4 mm. Al filter, TSD 30 cm.

In January, 1934, he had one treatment of 700 r to a 10×6 cm. lateral portal, using 198 kv., 30 Ma., 0.5 mm. Cu filter, 50 cm. TSD.

In July, 1934, he received 800 r to a lateral

tender, and the overlying skin showed the effect of previous irradiation by dryness, depigmentation and telangiectasia, and marked fibrosis. There was atrophy of the anterior portion of the arm; all movements about the



FIG. 15. Case 8. Partial healing of the cystic area, four years after irradiation of the lesions in Fig. 14.



FIG. 16. Case 8. Osteogenic sarcoma developing in the lesion shown in Figs. 14 and 15, nine years after irradiation.

portal, and from June, 1937, to October, 1937, six treatments were given to the lateral portal with an interval of two months between the first and second groups of three treatments each. These treatments in 1934 and 1937 were with 200 kv., 0.5 mm. Cu filter, 35 cm. TSD, 6 cm. portal. A moderate degree of healing followed as shown in Fig. 15.

In all, it has been estimated that the center of the tumor received a total dose of 5580 r in four years.

He remained symptom-free for the next nine years and joined the RCAF as a pilot, remaining on active duty for four years. In June, 1946, he fractured the left humerus again after a trivial blow. The arm was placed in plaster but failed to show bony union. Roentgenograms revealed calcium deposits in the soft tissues. The condition of the arm became progressively worse and more painful. He was admitted to Memorial Hospital on September 7, 1946. On examination the left upper arm was markedly swollen and

shoulder were markedly limited. (Fig. 16.)

On October 9, 1946, an open biopsy was reported as osteochondrosarcoma, fairly low grade. Accordingly, on October 18, 1946, an interscapulothoracic amputation of the left upper extremity was performed; the specimen confirmed the original biopsy diagnosis.

In May, 1947, a lump appeared beneath the scar near the point at which the clavicle had been divided with the Gigli saw at the time of the amputation. The patient was re-operated upon May 5, 1947, and the clavicle again severed near the sternal notch so that the mass could be removed as a whole. Report of this specimen showed it to be microscopically similar to the humeral lesion, i.e., chondrosarcoma. Another recurrence was excised in October 1947. Patient died of mul-

tiple metastases January 8, 1948.

Interval between last irradiation and sarcoma formation: nine years.

Case 9. R. W., female; 26 years old when sarcoma developed. Admitted to Memorial Hospital March 28, 1943.

In 1930, at the age of 13 years, the patient had roentgenograms made of her sinuses for unremembered symptoms. There was "an area of dense opacity situated just lateral to the left maxillary sinus. The left maxillary sinus is clouded and the inferior and lateral walls are indistinct. The orbital ridge on the left side appears elevated and indistinct."

Between April, 1930, and December, 1931, she received treatment over the left maxillary area. The factors were 200 kv., 0.5 mm. Cu filter, 60 cm. TSD. The exact size of the field is not known but appears to have been about 50 cm. square. The total air dose was 3370 r, the tissue dose at 2.5 cm. depth was approximately 3600 r.

She remained asymptomatic for thirteen years; then in February, 1943—seven weeks after having been delivered of a normal child—she began having pain in the left upper gum and the teeth in that area. A dentist took roentgenograms of this region and a biopsy was performed. The diagnosis at Memorial Hospital was osteogenic sarcoma.

A roentgenogram on March 17, 1943, showed "the maxillary sinus to be very much expanded and less clouded. The medial wall is not visualized and in the previously described density there are many small areas of translucency, located chiefly at the outer and superior portions of the density. The inferior and anterior border (on lateral views) appear thinned out and destroyed. Both films show soft tissue bulging over the left maxillary sinus."

Physical examination showed diffuse swelling of the left maxillary area with postirradiation skin changes of depigmentation, telangiectasia, and thickening.

On April 2, 1943, the left external carotid artery was ligated, followed by resection of the left maxilla.

Gross pathological description: "The inferior surface of the maxilla is intact. Just above the two bicuspid teeth, there is a punched-out ulcer (biopsy site) which measures 2 cm. in diameter and penetrates through the gum and bony lateral wall to a depth of over 1 cm. The floor of this ulcer is grayish and necrotic. The bony lateral and medial walls of the maxilla are almost completely absent except for a small portion of medial wall. Attached to the floor and side walls of

the antrum is a fleshy tumor, $3 \times 4 \times 7$ cm., excision of which seems complete. The tumor shows lobulation and except for the anterior surface which shows variegated red and white color, is homogeneous with a gelatinous appearance.

"Microscopic Diagnosis: Osteogenic sarcoma."

From April, 1943, to July, 1945, she had various stages of plastic repair of the scar, but there have been no signs of recurrence; her last follow-up visit was on November 27, 1946.

Interval between last irradiation and sarcoma formation: thirteen years.

Group III. Normal Bone Underlying Roentgen-Ray Treated, Soft-Tissue Lesions.

Case 10. K. P., female; 57 years old when sarcoma developed. Admitted to Memorial Hospital February 7, 1943.

Her previous history follows: She had had a left radical mastectomy in July, 1935, for a solid and alveolar carcinoma of the left breast metastatic to one node. She received postoperative irradiation; 198 kv. machine, 0.5 mm. Cu. filter, 50 cm. TSD, 13×13 cm. portals; 750 r were given daily, to each of three portals described as anterior and posterior supraclavicular, and direct axilla. She had a total of 2100 r to each of the first two portals and 1900 r to the third. The first treatment was in September, 1935, and the last in October, 1936. Calculations showed the tumor dose to the second rib to be 4480 r. Convalescence was uneventful. In January, 1943, she had a malignant melanoma removed from the skin overlying the right deltoid muscle and lymph nodes containing metastatic melanoma were removed by right axillary dissection in December, 1944.

She was asymptomatic until September, 1945, when a recurrence of the melanoma on her right arm was excised. In October, 1947, she began to notice a painless swelling in the left upper anterior chest (Fig. 17). Examination of this area showed an elliptical mass about 12×10 cm., elevating the skin about 6 cm. and apparently fixed to the underlying bony structures. The skin overlying this and the clavicular area in this site showed slight to moderate depigmentation, fibrosis, and telangiectasia. In October, 1947, an open biopsy was performed on the mass which the pathologist diagnosed as "osteogenic sarcoma following roentgen irradiation of bone (not a metastases from either breast or melanoma.)" The wound healed and no further treatment was given.

Interval between last irradiation and sarcoma formation: eleven years.

The series of roentgenograms show the



FIG. 17. Case 10. Tumor of the second rib arising in the area heavily irradiated eleven years previously following radical mastectomy. Note the biopsy incision and marked telangiectasia of the surrounding skin. Microscopic report: "osteogenic sarcoma following roentgen irradiation of bone."

change from a normal rib to a fractured rib, and finally, to an osteogenic sarcoma. This case is quite similar to Hatcher's third case in that prophylactic irradiation was given after a radical mastectomy and a rib was the site of the sarcomatous change. He points out with Shields Warren, and this case would certainly substantiate that contention, that some individuals are more prone to develop numerous cancers and that the susceptibility to carcinogenic influences has a much lower threshold in these people. It should be mentioned that a personal communication from Dr. Frank Adair of the Breast Service of Memorial Hospital, revealed that an estimated 3000 to 4000 patients have had postoperative

irradiation without another known case of an osteogenic sarcoma developing, although roughly 40 per cent of them lived five years or more.

Case 11. E. B., female; 9 years old when sarcoma developed. Admitted to Memorial Hospital February 12, 1946.

The family history includes several great uncles who died of Hodgkin's disease. Three grandparents died of carcinoma, one great aunt had sarcoma and a great uncle had carcinoma; the sites of these are unknown.

At the age of 2½ years, her right eye was removed at another hospital for a retinoblastoma. Six months later the left eye appeared involved and the patient was referred for roentgen-ray therapy. She received 9600 r \times 2 to a left temple portal and a nasal portal directed towards the posterior chamber of the left eye, 400 r daily: 200 kv., 0.5 mm. Cu filter, 60 cm. TSD, 2.5 cm. portal. In addition, she had 2400 r to these portals three times weekly with the same dosage and factors for a total of 2400 r to the right nasal portal and also, in treatment ending April, 1941, a total of 2400 r to a supra- and 2800 r to an infraorbital portal; the factors and dosage were as before. The total dosage to the portals was: Left temple, 11,600 r; right nasal, 11,200 r; left infraorbital, 2800 r; and left supraorbital, 2400 r. The tumor dose to the vicinity of the lacrimal bone and ethmoid area on the left was approximately 16,000 r in 1939 and 9000 r in 1941. Her present admission stems from complaints of painless swelling of the left eyelids and the protrusion of a nasal mass through the left nostril.

Physical examination showed an atrophic and whitish-gray left eye, an artificial right eye. There was tenderness and moderate swelling at the left inner canthus of the eye. The left nasal passageway was plugged by a grayish, lobulated mass, diagnosed by biopsy as an osteogenic sarcoma with a chondromatous element. In February, 1946, the left external carotid was ligated, the left maxilla and infraorbital plate excised and the left orbit exenterated. In May and June, 1946, recurrences were excised from the ethmoid-bone region. She finally died. There were obvious recurrences, the growth filling both nares, both orbital cavities, and the entire mouth. Autopsy revealed recurrent osteogenic sarcoma of the left orbital plate (frontal bone) involving both orbits, the nasal cavity and the cranial cavity. The right orbital plate was free of tumor. No residual retinoblastoma was found. (See Fig. 18.)

Interval between last irradiation and sarcoma formation: five years.

The initial diagnosis of retinoblastoma has

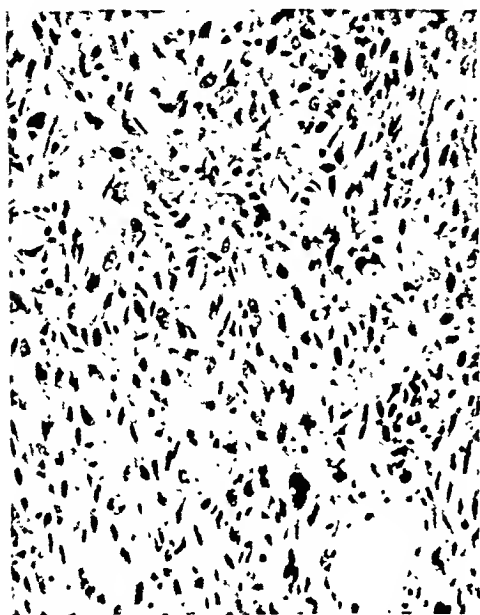


FIG. 18. Case 11. Microphotograph showing osteogenic sarcoma arising in the ethmoid, five years after irradiation for recurrent retinoblastoma. No residual retinoblastoma was found.

been substantiated. The early roentgenograms of the child's skull show no bone lesions. A large amount of irradiation was given when the second retinoblastoma developed on the left. She developed an osteogenic sarcoma five years after the last treatments. The tumor dose was figured for the left lacrimal bone, but the same figures obtain for the left ethmoid bone, which probably received the brunt of the cross-fire irradiation in this area.

CONCLUSIONS

Development of bone sarcoma in bone that has been exposed to heavy doses of roentgen-rays or radium is an uncommon sequel. It may take place in a benign tumor or in normal bone. A latent period of from five to more than twenty years following exposure is required for development. It is seldom seen after moderate doses and probably requires a tissue dose of 3000 r. There is little uniformity in the dosage, however, for sarcoma ensued in case 6 after a tumor dose of 1550 r. No satisfactory explanation can be offered of

why so few bone sarcomas develop in the thoracic cage following the heavy irradiation consequent upon radical mastectomy for breast cancer, or in the pelvic bones after irradiation for uterine cancer. It may be that such developments have been confused with metastatic carcinoma. Nor has sarcoma been observed frequently in the intensely irradiated facial bones and jaws in patients treated for cancer of the mouth, jaws, neck, etc. Perhaps few of the latter survive sufficiently long.

When a patient returns with complaints of pain, with or without swelling, in an area that had been treated by irradiation for a benign bone lesion five or more years previously, immediate suspicion of malignant change should be aroused. Roentgenograms should be made at once and biopsy material obtained, preferably by aspiration, to avoid incision of the irradiated tissues.

The tardy development of bone sarcoma after irradiation is another reason for believing that roentgen-ray therapy is not ordinarily to be recommended for nonmalignant tumors of bone. Although its incidence, judged by the paucity of references in the literature, is small, it has most serious implications when it does occur. Treatment should consist in immediate wide surgical removal either by resection or by amputation.

We believe that more cases of this sort will be reported as the condition becomes more widely recognized; also that in succeeding decades it is likely to become increasingly rare as the profession restricts the use of roentgen-ray therapy to malignant neoplasms. Since giant-cell tumors have inherent tendencies to undergo alteration in their histologic appearance and clinical behavior it seems advisable to avoid, wherever possible, the use of an agent (roentgen-rays) that may of itself provoke malignant change.

SUMMARY

Histories are presented of eleven patients in whom osteogenic sarcoma developed in irradiated bones six to twenty-two years after roentgen or gamma-ray therapy.

The literature of similar cases is reviewed and the role of irradiation in the production of malignant changes in bone is discussed.

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FIBROSARCOMA

The Malignant Tumor of Fibroblasts

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MOST of the surveys of the malignant tumors composed of supportive tissues place the fibrosarcoma at the top of the list in frequency. It is natural therefore to ask—what is a fibrosarcoma? how malignant is it? and how does one recognize it? The fibrosarcoma is reputed to be a tumor composed solely of fiber-forming connective-tissue cells and, according to reports, highly malignant except when it develops in the skin. One would suppose that its microscopic recognition should be easy. Yet actually a perusal of the literature makes it obvious that there are many different and conflicting conceptions of it, and that a variety of lesions both benign and malignant have been included under the term that do not belong there and that serve only to obscure and confuse our understanding of it and make its recognition one of the most baffling problems of oncology.

There are many reasons for this which must be thoroughly understood before one can undertake the problem of elucidation. In the first place it is necessary to realize that the mesenchyme from which most of the supportive, reticulo-endothelial, and hematopoietic tissues are derived is a vigorous and versatile tissue that does not always reproduce in tumor form a single, fixed tissue pattern but sometimes makes tumors composed of two or more cellular types.¹⁰⁰ For example, liposarcomas and rhabdomyosarcomas both are very prone to have portions of the neoplasm composed of what seems to be fibroblastic tissue and this may be so marked that recognizable lipoblasts and rhabdomyoblasts can only be found after painstaking search. The synovial sarcoma is always made up of an inextricably intermingled conglomeration of synovio-

blastic and fibrosarcomatous elements. If the fibrosarcomatous elements predominate, a small biopsy specimen might easily fail to show the true nature of the neoplasm. There is little cause for wonder therefore that many malignant sarcomas of other sorts have been reported as fibrosarcomas, or else the reporter has confessed his inability to recognize the nature of the tumor at all by using the term "spindle cell sarcoma." It is an utter waste of paper to report a tumor by this title unless the description and illustrations are so good that an expert oncologist, aided by the clinical history, can recognize the true nature of the growth from them. A second source of confusion stems from the fact that the schwannian cell, a neuroectodermal derivative, is capable of forming reticulin (i.e., delicate connective-tissue fibers that are blackened by silver connective-tissue stains) in tumors and therefore may simulate a fibroblast, so that the rather rare malignant schwannoma may be mistaken for a fibrosarcoma. The whole problem of the fibrosarcoma was rendered enormously more confused and complex by the conception of the "neurogenic sarcoma," a name introduced by the late James Ewing who supposed that a great many deeply placed, spindle-cell tumors stemmed from peripheral nerves. This conception was publicized by Quick and Cutler and Stewart and Copeland of the Memorial Hospital. Since they did not give specific criteria for recognizing the "neurogenic sarcoma" the name has come to be applied to almost any rather cellular spindle-cell tumor. Thus neurogenic sarcoma is used by many pathologists and oncologists in the Americas without discrimination and has almost as little meaning as the purely morphological term "spindle cell sarcoma" which has cluttered the literature of the world from the beginning of cellular pathology. It is to be deplored that such a careful

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Received for Publication, December 2, 1947.

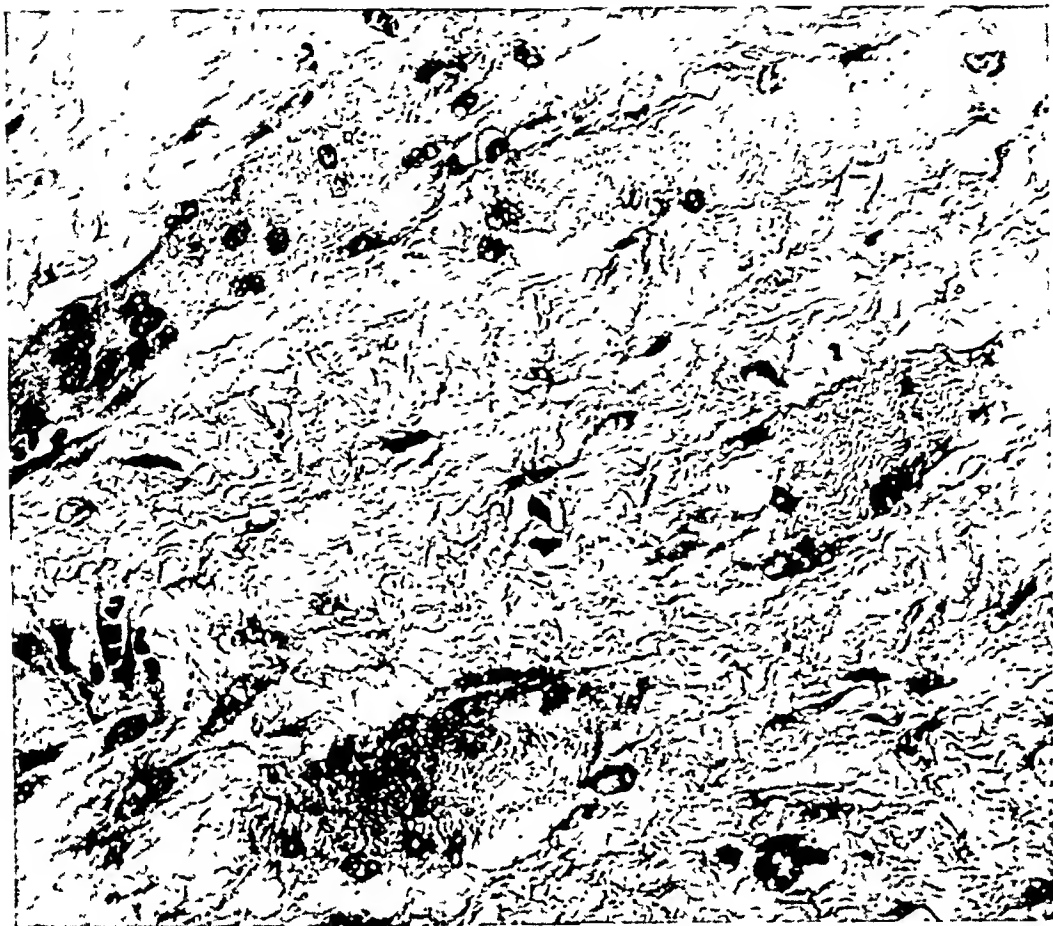


FIG. 1. *Desmoid tumor, 5 × 3 × 2.2 cm., involving the rectus abdominis muscle of a twenty-six year old woman who had borne one child and had had two miscarriages. There had been no recurrence eleven and a half years after excision. The photomicrograph shows a growth of almost adult fibrous tissue that has infiltrated between and separated the muscle fibers. × 470.*

observer as Shields Warren has expressed the opinion that the neurogenic sarcoma is an entity which can be recognized²⁰⁶ and Chandler Foot, too, has given it recognition using the term "neurogenous sarcoma." I have perused the papers of these gentlemen with painful attention but have failed to discover what cell type or types produce this tumor, what structure it has by which it may be identified, or indeed any exact or concrete information about it. Some factual knowledge does, indeed, exist about tumors derived from peripheral nerves including the rather uncommon malignant schwannomas. These can be recognized by certain histological features but best of all by tissue culture, since the Schwann cell grows in vitro in a specific fashion.¹⁴⁷

There are many malignant fibroblastic tumors that involve nerves in their infiltrative growth. Conceivably some of these may even originate from the mesodermal elements of a peripheral nerve, but, if so, there is as yet no way in which such a tumor can be distinguished from any other tumor of mesodermal derivation; for, in vitro, the fibroblasts of a nerve sheath do not have specific growth characteristics by which they can be recognized and segregated from other fibroblasts.¹⁴⁶ consequently there is no basis for the supposition that there is a special variety of nerve fibrosarcoma that can be designated a "neurogenic sarcoma." Thus, since the term is a chimera, it will serve only as a bar to progress as long as it continues to be used.



FIG. 2. The same case as Fig. 1. Laidlaw silver reticulin stain shows the dense tangle of collagen and reticulin fibers separating striated muscle fibers. $\times 470$.

FIBROUS HYPERPLASIA AND NEOPLASIA

Unfortunately the foregoing by no means exhausts the roster of all of the difficulties that face the oncologist in his attempts to erect criteria for the recognition of malignant fibroblastic tumors. There are a variety of conditions and circumstances that lead to the proliferation of fibroblastic tissue. It is not the intention here to review all of these since this would necessitate a separate monograph. Thus, for example, what Klemperer calls diseases of the collagen system as well as many poorly understood fibroses, such as Peyronie's disease of the penis, will be omitted because, so far as I am aware, they do not produce clinical or histopathological changes that are apt to be confused with or lead to the formation of fibrosarcomas. Only those lesions will be dealt with that lead to the proliferation of fibroblastic tissue in such a fashion that tumors are formed. Most of these tumors in-

filtrate surrounding tissues as they grow; they may be more or less cellular with greater or lesser quantities of intercellular connective-tissue fibers. Are they true neoplasms or pseudo-tumors? Are they benign or malignant? These are questions which have often puzzled those reporting them so that they appear in the literature under a variety of terms. In order to approach the subject, each one of these conditions must be reviewed and its exact relationship to malignant connective-tissue tumors discussed.

The best known of these proliferations is the *keloid*. This occurs in two manifestations. The more common, which is usually but not invariably found in the Negro, consists of an overgrowth of scar tissue in manifest or occult cicatrices in which many of the collagen fibers undergo a peculiar and apparently specific form of swelling. This is the true keloid; it is not regarded as a malignant neo-

plasm since it does not metastasize or kill and, strangely enough, seems to affect only the superficial cicatrices and not those in mucous membranes or the deeper organs and tissues of the body.

There is another type of proliferative activity in scar tissue that is much more difficult to evaluate, for it is not especially associated with the Negro and does not show the specific swelling of its collagen fibers. The best-known example of this is the *desmoid* tumor found most commonly but not invariably in the abdominal-wall muscles and fasciae of women who have borne children. It consists of a proliferation of scarlike tissue in the form of a nodule that infiltrates surrounding muscles and fasciae and may grow to a very considerable size although generally it averages about 6×4 cm. actual measurement after excision. The statistics of our own cases approximate those of other clinics. There were twelve cases all in women, two of whom were colored. Their ages at the time of treatment varied from 23 to 38 years except one woman who was 45 years old. All of the women were married; eight had borne children, two had not, and information on this point is lacking for the others. In every case the tumor involved an abdominal muscle. All were excised; none is known to have recurred or metastasized. Four patients were not followed; two were symptom-free less than five years, three more than five years, and three more than ten years (Figs. 1 and 2).

The literature furnishes some additional information. Apparently similar growths can develop in childhood. Waugh described one in the rectus abdominis muscle of a 5-year-old boy who had injured the region in a fall at the age of $3\frac{1}{2}$ years; and Grenet and Mézard reported one that grew between the rectus muscles of a two-year-old girl. There have been general reviews of the abdominal-wall fibrous growths by Mankin, by Mason, and by Mead and Brewster. Mankin's review is the most extensive including 629 cases which were recorded as follows: 423 fibromas, 155 fibrosarcomas, 4 myosarcomas, 2 angiosarcomas, 2 myxomas, and 43 unclassified sarcomas; 544 patients were women

and 90 per cent of them were parous. He found that the majority of the so-called true sarcomas were in men. It is quite obvious that such a group includes both desmoids and true neoplasms. This is true also for the Co-



FIG. 3. *Fibrosarcoma of the abdominal wall. The eighth recurrence, twenty years after onset. Two years later the patient died of local spread.*

lumbia University group of cases, for in addition to the twelve desmoids there were thirteen other cases of fibrosarcomas of the abdominal wall that pursued a course similar to fibrosarcoma elsewhere except that none metastasized. Six of these were in men. One or more recurrences are known to have occurred in five patients; and two of these cases, both of which were in males, had a known or suspected fatal outcome. One was in a 43-year-old Italian who had a growth in the region of the inguinal ligament. During a period of two and a half years, five attempts were made to get rid of it but without success. At the end of that time he was considered inoperable and elected to return to Italy, presumably to die. The other was in an American male. In 1897, at the age of 33 years, a small lump appeared in the midline between the symphysis pubis and the umbilicus following some unknown trauma. After six months an unsuccessful attempt to excise it was made at another hospital. During the next twenty-two years eight more attempts were made to remove the constantly recurring tumor, all of which failed as did an

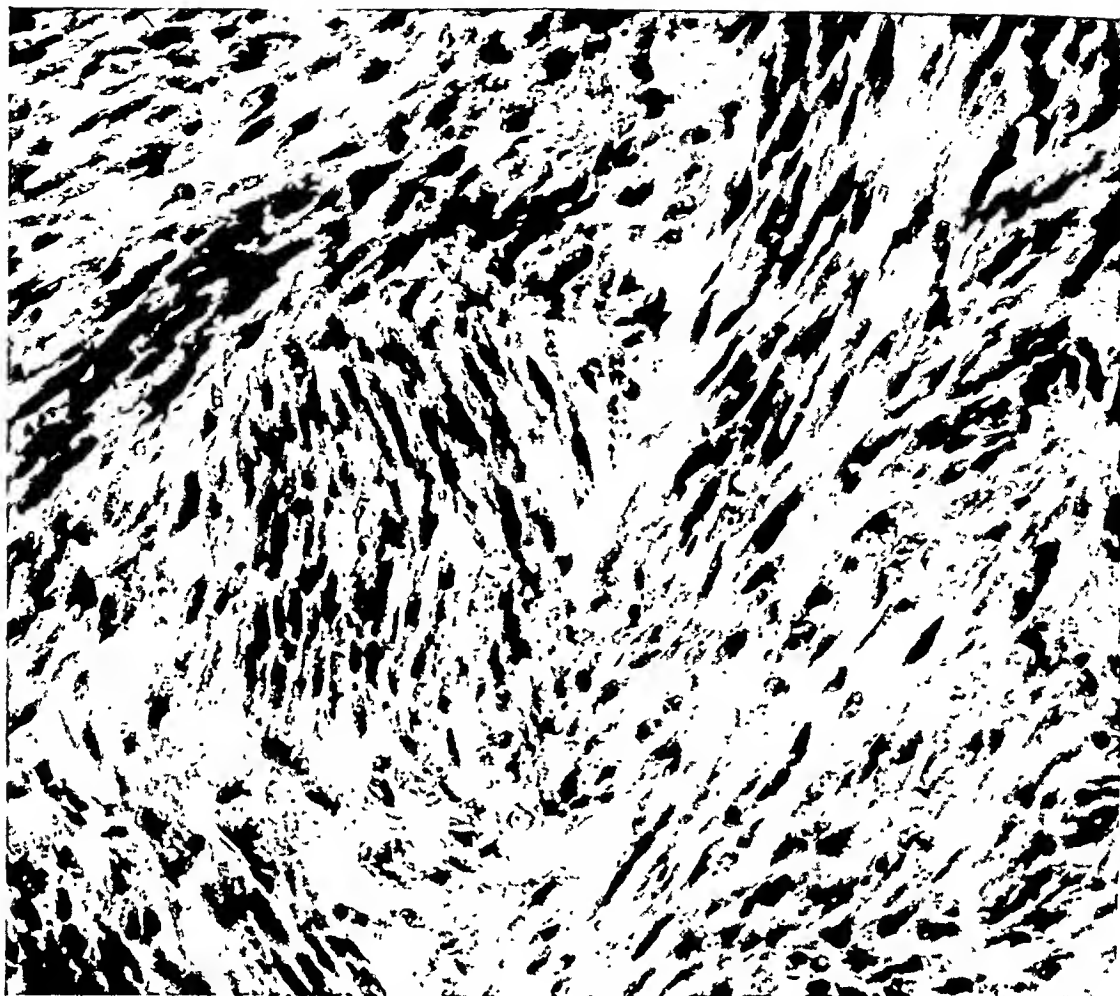


FIG. 4. *Fibrosarcoma of the abdominal wall. The same case as Fig. 3. Photomicrograph (H. and E. stain) showing tumor cells in bundles; the spacing of the cells indicates the presence of many intercellular fibers. The dark color of many nuclei is due more to overstaining of the old thick section than to nuclear hyperchromatism. No mitoses shown—they were rare. $\times 470$.*

attempt to treat him with Coley's toxins. He finally died in 1919, at which time the growth contained sinuses and had invaded the lumbar region and the peritoneal cavity (Figs. 3 and 4).

Is it possible to differentiate true neoplasms such as these from desmoid tumors which are questionable neoplasms? Except for the fact that the desmoid tumors developed in the muscular tissues of the abdominal wall of females while the true neoplasms, (all of which, by the way, were well differentiated) developed in other tissues of both men and women, I do not believe that it can be done with assurance purely on the basis of the histopathology. The apparent differences will be discussed later.

Are there growths similar to desmoids in muscles and aponeuroses in the body elsewhere than in the abdominal wall? Mason, in reporting fifty desmoids from the Mayo Clinic, found ten of them in other regions and Tuta and Fischman reported an example in the sacrospinalis muscle. No doubt this is true; but, in the Columbia University collection, I have felt it impossible always accurately to distinguish such growths from true neoplasms by histological methods. Certain it is, however, that such well-differentiated growths very rarely metastasize and if completely removed do not recur (Fig. 21).

Somewhat akin to the desmoid tumor in the muscles and aponeuroses of the abdominal wall are the nodular fibrous growths in



FIG. 5. *Dermatofibrosarcoma protuberans* of the back (see text).

the skin which have been called by many names the most popular being *dermatofibrosarcoma protuberans* (Hoffmann) and *progressive recurring dermatofibroma* (Darier). This slowly growing tumor elevates the skin in a single nodule in the Darier type and in multiple, often coalescing, hard nodules of a reddish hue in the Hoffmann variety. Histologically the growth looks like a well-differen-

tiated fibrosarcoma. It is usually restricted to the skin and subcutaneous tissue but often extends in thickened plaques far beyond the visible nodules so that one must make a very wide excision to remove all of it. Since this has seldom been done in the past, recurrences are frequently reported. In the Columbia University collection there are no cases with metastases recorded. Beck, Eliascheff, Hoffmann, McMaster, Nicolau, Pautrier and Woringer, Scomazzoni, and Willis among others all have stressed the recurring feature of these tumors but were unacquainted with metastases. It is apparently possible, however, for fibrous tumors of the skin to produce metastases. Bezecny, in 1931, reported three patients with protruding progressive dermatofibrosarcomatosis and stated that metastasis was unknown. In a second article in 1933 he announced that one of the three had died with metastases in the lungs while in the peribronchial lymph nodes of the same case there were carcinomatous metastases from an unknown site. Sciacchitano also described a skin fibrosarcoma with pulmonary metastases. Hertzler reported lymph-node metastases from one of his cases of skin fibrosarcoma. Simmons stated that of twenty-four skin fibrosarcoma cases, from the Collis P. Huntington Memorial Hospital, four were fatal; since the cases are not reported in detail, one can-

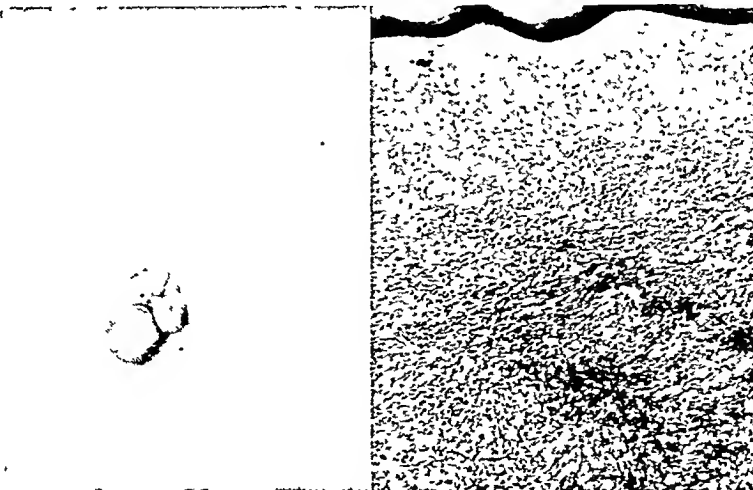


FIG. 6. The same case as Fig. 5. The tumor nodules and the halo about them were reddish. The halo indicates the extent of spread. The low-power photomicrograph shows how the tumor, by pressure, thins the epidermis and irons out the rete pegs.

not be sure that these are neoplasms truly primary in the skin. All authors stress the long duration and slow growth of these tumors. This is admirably illustrated by Figs. 5 and 6 which show a characteristic case involving the interscapular region of a 34-year-old woman. The nodules and surrounding halo were reddish and had been growing for seven years. After very wide excision she was followed for thirteen years and two months without recurrence. As an example of slow growth and recurrence there may be cited the case of a colored girl who apparently had a nodular growth in the skin of her forearm which appeared at the age of 4 years, grew slowly, and was removed at the age of 25 years. It reappeared after two years and was again removed at the age of 48, when it had attained a size of 7×4 cm. Eight years later, at the age of 56 years, no further recurrence had taken place. Histologically these growths look somewhat more like differentiated fibrosarcomas than they do like hypertrophied scar tissue or keloids. Sometimes, but infrequently, they have a whorled appearance (described in detail later) that makes them resemble the tumor called variously sclerosing hemangioma, neurofibroma, or fibrous xanthoma. In my experience these skin fibrous tumors are composed basically of fibroblasts and connective-tissue fibers and have no relationship to any of the tissues that form the nerve sheaths. Moreover, whatever blood vessels or phagocytic cells containing lipid or blood pigment may be present can probably be regarded as coincidental and not essential parts of the growth. It is probable, as has been suggested by Wilson, that size and persistence of infiltrative growth are the best criteria for deciding whether or not to call these tumors fibrosarcomas.

Palmar and Plantar Fibromatosis. Another lesion that sometimes simulates the appearance of the desmoid histologically and has even been mistaken for a fibrosarcoma is sometimes associated with Dupuytren's contracture of the palmar and plantar fascia. In these cases the proliferation of fibroblastic tissue infiltrating the fascia occurs to such a degree that tumor-like nodules may be formed. When they are made up of cellular interlaced

bands of fibroblasts and collagen fibers, such growths can look very much like tumor formation. Clay noted it and described it as fibroma; the same condition is shown in Horwitz's illustrations although he does not call attention to it. It is probably very seldom mistaken for true neoplasm in the palm when it is accompanied by the characteristic contractures; but when the plantar fascia is involved and there is no contracture, differentiation from true neoplasm may be impossible and incomplete excision has led to repeated recurrences and even amputation of a foot.^{37, 38} Under such circumstances one cannot avoid the belief that a true fibrosarcoma has been formed although apparently not a metastasizing one. In illustration the following case may be cited:

At the age of eighteen years, D.H., a Scotch girl, stepped on a sharp rock which caused some pain in the sole of the foot but no gross evidence of contusion or abrasion. Two months later a swelling appeared that grew painlessly for seven years. It was then removed elsewhere and called fibroma. In five weeks it reappeared and seven months later was re-excised; four roentgen-ray treatments were then given. Recurrence in five months led to a third excision two months later. Rapid recurrence finally necessitated amputation through the junction of the middle and lower thirds of the leg at the age of 27 years. She was without evidence of disease ten years after this last procedure.

This growth was exceedingly well differentiated in all of its manifestations and apparently started in and around the plantar fascia.

The tale of these tumor-like fibrous proliferations is still incomplete until the rare and peculiar congenital condition called *progressive myositis fibrosa* (Meyenburg), or *hereditary polyfibromatosis* by Touraine and Ruel, has been cited. In this unusual condition successive areas of subcutaneous and intramuscular scarlike connective tissue form that grow and increase by infiltration so that microscopically it sometimes simulates a desmoid or a fibrosarcoma. The process may form successive nodules in all parts of the body, or it may affect the tissues of a single extremity. It starts generally in the first two or three years of life but may appear in adults. Rarely the

affected areas become calcified or ossified in which case it is called progressive myositis ossificans.²⁰⁴ The infiltrating fibrous growth may contract, so that if the neck is affected, the picture of congenital wry neck is produced. It is very easy for the pathologist unacquainted with this condition to suppose he is dealing with an infiltrating fibrosarcoma. Whether or not such peculiar fibroses can produce malignant tumors is unknown to me; if any has been reported I have not found the reference. Touraine and Ruel in discussing this condition point out that Janssen, in 1902, grouped under the term "fibroplastic diathesis" Dupuytren's contracture, induration of the corpora cavernosa, keloids, gout, and arthritis deformans. Since that time many other fibromatoses have been added and they feel that heredity plays an important role in the etiology which, however, remains obscure.

The survey so far has seemed to indicate that fibrous growths of a proliferative nature that may be pure hyperplasias, benign tumors or malignant sarcomas can develop either spontaneously, or as a result of irradiation, or of some mysterious inherent cellular peculiarity in scar tissue. It will be well to examine the evidence concerning this relationship in more detail.

Irradiation Fibromatosis. Irradiation damage of skin and mucous membranes is recognized as an important etiological factor in the production of malignant epithelial tumors. This mode also produces changes in the fibrous tissue sometimes resulting in the formation of atypical and monstrous fibroblasts. Rarely this damaged scar tissue proliferates, forming tumor-like masses. In the literature there are reports of such tumors forming in skin, subcutaneous tissue, or buccal mucosa overtreated by irradiation for lupus vulgaris,^{1, 2, 45, 59, 141, 156, 177} for deeper tuberculosis,^{95, 110} for other tumors,^{15, 45, 82, 86, 178} for hypertrichosis,¹¹¹ and for keloidal burn scars.²¹⁶ In the Columbia University group there were four such cases; two were treated by roentgen-ray irradiation for hypertrichosis, one for psoriasis, and one for an undetermined skin lesion of the dorsum of the penis. In these four cases the tumors were all

small, there was no evidence of metastasis or recurrence following removal, and it was questionable in my mind whether or not they should be called fibrosarcomas. However, recurrences following attempted removals are frequent in a number of the reported cases; nine out of sixteen died and four^{1, 141, 156, 216} had metastases. So it cannot be doubted that truly malignant fibrosarcomas may develop in tissues damaged by irradiation, but the incidence must be very small. The interval between radiotherapy and tumor development varied from one-and-a-half to twenty-seven years but was commonly more than five years. One of our patients, the skin of whose lower extremity had been badly damaged by irradiation for psoriasis, developed both squamous-cell epithelioma and a fibrosarcoma-like tumor.

Cicatricial Fibromatosis and Fibrosarcoma.

It has already been indicated that fibrous tumors can develop in the scars from trauma, burns, or infections of one sort or another, but if one takes the sum total of all cicatrices, the actual number that develop fibrosarcomas is so minute that Melzner has doubted if the relationship is anything more than fortuitous. He was interested especially in the number of sarcomas developing in wounds received in the First World War which he believed to be extremely few. He reported one, in a cicatrix in the thigh, that developed eleven years after the wound was received. He supposed that sarcomas developed in scars only if the individual had a special predisposition. Another case in a war wound of the hand was reported by Thies, and one in the chest wall by Clavelin and Lacaux. Other reported types of injury preceding sarcoma formation are: a punctured wound in the calf of a miner,¹³ a leg ulcer,⁷⁵ an osteomyelitis scar,⁹¹ the site of arsenic injection in which case the fibrosarcoma was found to contain traces of arsenic,⁹² an operative scar,⁸⁹ following a blow with several months elapsing before the tumor appeared,⁵⁴ and in a hematoma.¹⁷² This last case was questioned in discussion by Delbet who thought the tumor might have been present when the blow was received. The cases reported by E. Fahr, following a

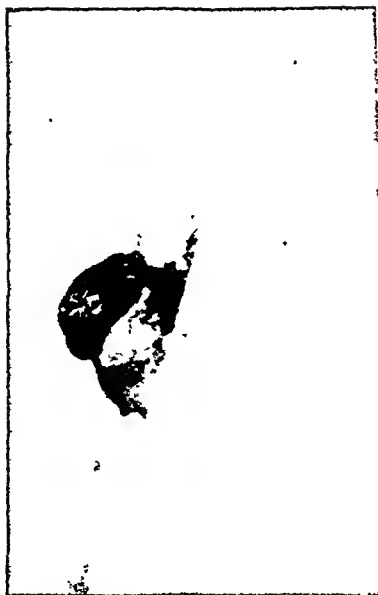


FIG. 7. *Fibrosarcoma in the scar of the interscapular region. The recurrence appeared thirty years after the tumor had been removed by Lord Lister (see text).*

horse bite, and by Fleming and Rezek in a burn scar seem to me to be liposarcomas rather than fibrosarcomas. It has already been pointed out that the desmoid tumors in the abdominal-wall muscles and aponeuroses of women very probably develop in the scar tissue formed from the stretching of these tissues during pregnancy.

In our own material, exclusive of desmoid tumors, at least thirty-six of the cases developed a fibrosarcoma in definite scar tissue or at the site of a former injury. They include some of our most fascinating and spectacular cases, two of which will be cited in illustration:

Case 1. C. S. was an Irishman born in May, 1852. When a boy he injured the interscapular region. At the age of 9 years a lump appeared in the scar; because of rapid growth it was excised at the age of 35 years without anesthesia or carbolic spray by Lord Lister in London. The wound was infected and the lump reappeared rapidly. It remained quiescent for thirty more years when

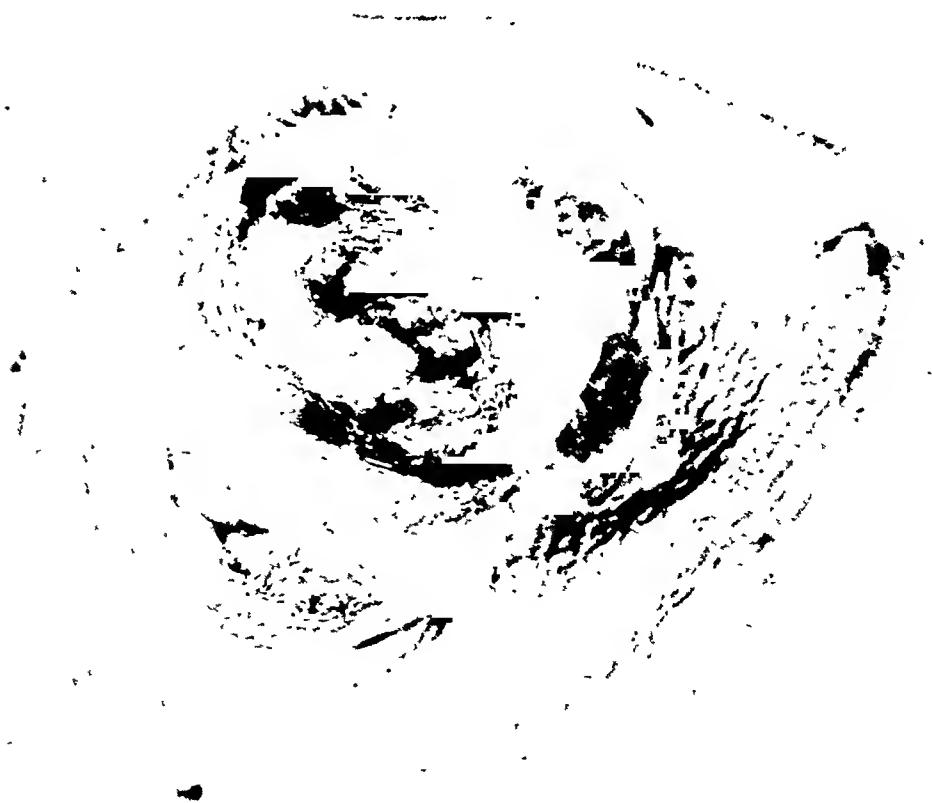


FIG. 8. *The same case as Fig. 7. This shows the generous and adequate excision of the recurrent tumor.*

again it grew rapidly to a diameter of 4.5 cm. and ulcerated. Then, at 65 years of age, the mass and surrounding tissue was generously excised at the Presbyterian Hospital by Dr. Bert Rulison. It was a well-differentiated fibrosarcoma. This operation was successful and there was no recurrence twenty-five years later when he was last seen by Dr. A. O. Whipple, at the age of 91 years (Figs. 7, 8, and 9), 82 years after the tumor was first discovered.

Case 2. C. O'C. (alias Soap Box Harry) who was a burglar of the variety known as "second story man" was shot in the lower inner aspect of the thigh with a .38 caliber revolver and sent to Sing Sing prison with a life sentence at the age of 27 years. Eleven years later a tumor appeared in the scar, and after four years of growth it was excised but recurred promptly. During the next eleven years, six local operations were done for constantly reappearing local recurrences. Finally the tumor grew to a large size, ulcerated

deeply, and almost surrounded the knee joint in its invasion. He was brought to the Presbyterian Hospital where a high thigh amputation was done. Thirteen months later he died at the age of fifty-three years with signs of pulmonary tuberculosis. As no autopsy was done, it is uncertain whether or not there were pulmonary metastases. The tumor was a cellular fibrosarcoma of medium differentiation with many mitoses and a number of bizarre enlarged spindle cells (Figs. 10, 11, and 12).

These cases illustrate the characteristics of the majority of scar tumors. Of twenty-four patients with scar fibrosarcomas that were followed, thirteen had one or more recurrences after excision. Two died with blood-borne metastases; one died with possible lung metastasis; one died and two were last seen alive with the tumor persisting. The remaining eighteen were without evidence of tumor

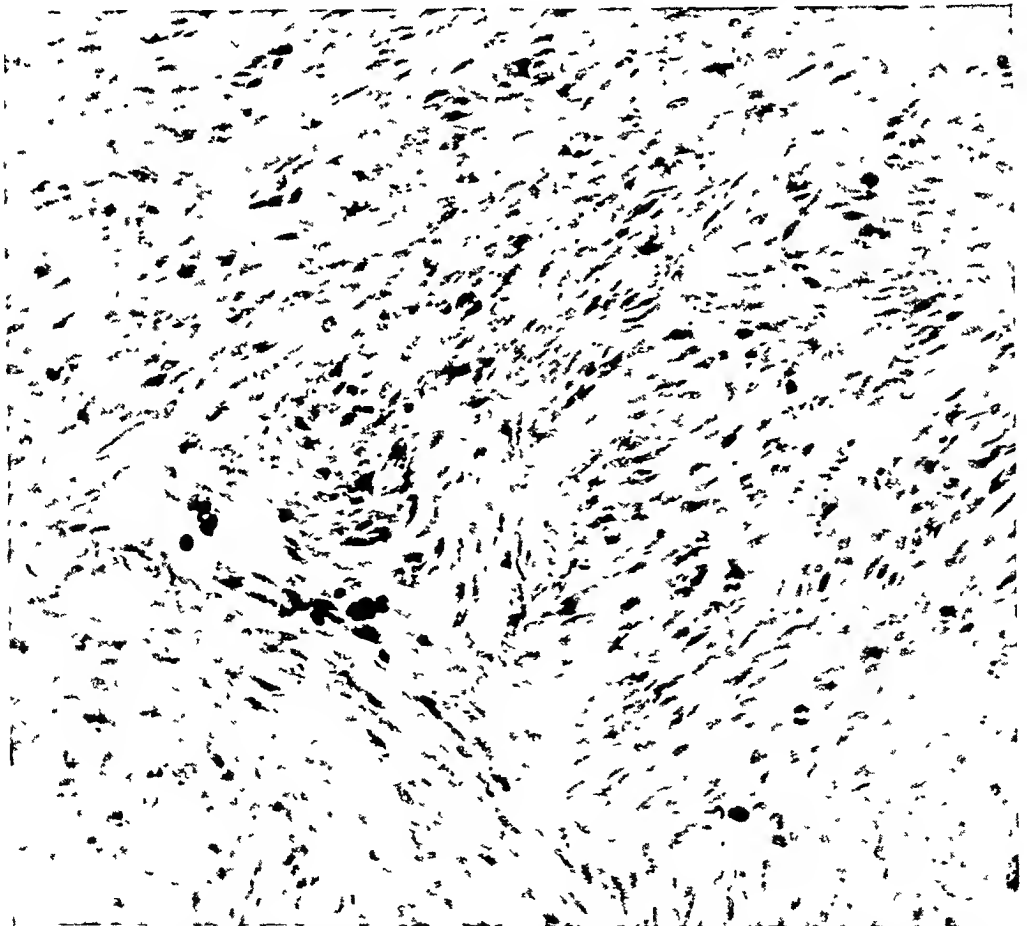


FIG. 9. The same case as Figs. 7 and 8. Photomicrograph of the tumor showing the interlaced bands of well-differentiated fibroblastic tumor cells. The spaces between the cells indicate the plentiful intercellular connective tissue fibers. $\times 470$.



FIG. 10. *Fibrosarcoma recurrent in the scar of an old revolver bullet wound of the thigh above the knee (see text).*



FIG. 11. *The same case as Fig. 10. The tumor bisected, with the patella and attached tendons reflected forward.*

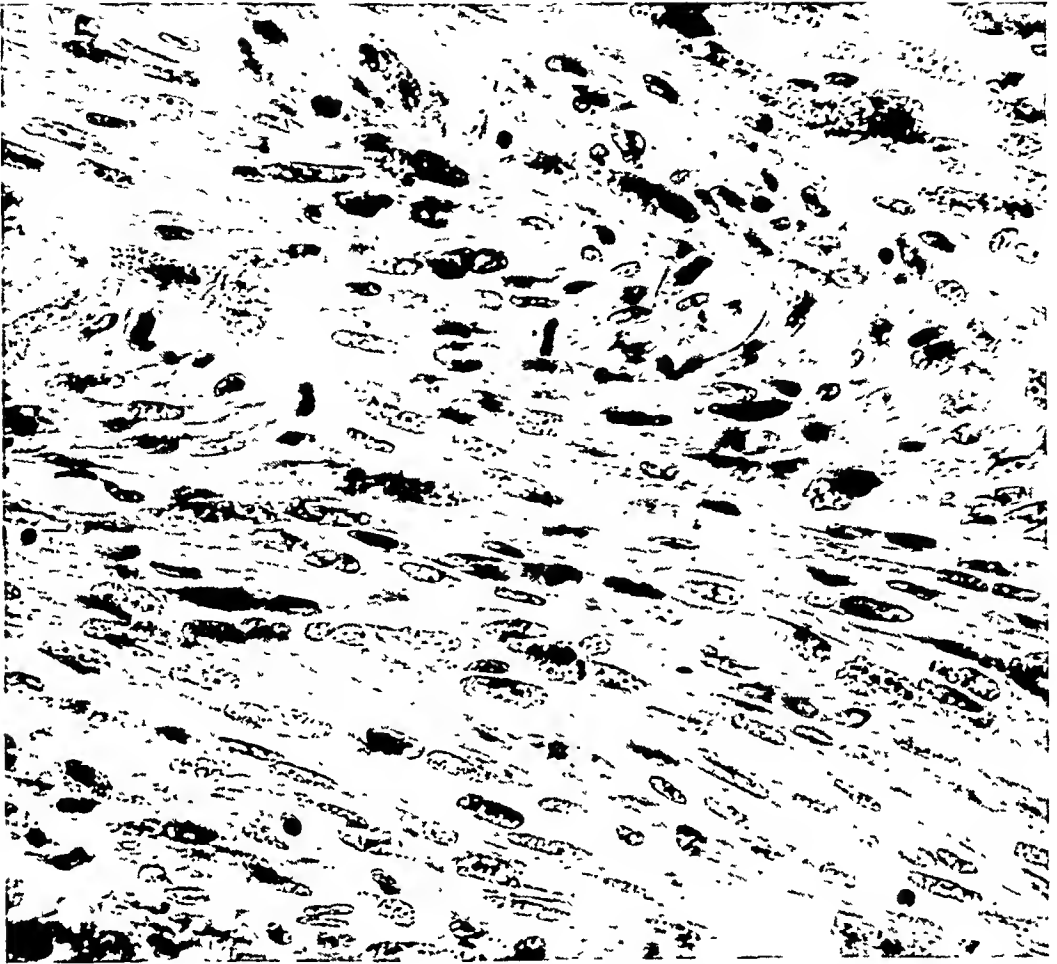


FIG. 12. The same case as Figs. 10 and 11. Photomicrograph shows some degree of anaplasia, hyperchromatism and cell irregularity. The close proximity of the cells, one to another, indicates the smaller number of intercellular fibers. The mitotic figure is an indicator of rapid proliferation and potential malignancy.

at intervals of from one to twenty-five years after the last successful removal. One of these died of intercurrent nephritis without evidence of tumor three years after excision. Had all the tumors been widely and extensively removed when first treated it is quite possible that all the patients would have been cured.

Fibroma. So far no mention has been made of the benign fibrous neoplasm or fibroma. Nothing illustrates better the complexities of the whole subject of malignant fibrosarcomas than the attempt to define a benign neoplastic fibroma. There are two varieties of lesions in the skin called fibromas. One is the pedunculated soft fibrous tag of very variable size, covered with epidermis and

having a fibrous or fibrous and fatty core resembling the corium without any accessory skin structures in it. Obviously these are malformations without any histological resemblance to neoplasms and only because they can display a certain degree of autonomous growth can they lay claim to the name fibroma. They have no relationship to malignant tumors. The other variety is an intradermal infiltrating growth of scarlike fibroblastic tissue in the skin and sometimes the subcutaneous tissue. This may be relatively avascular or it may be quite vascular and contain varying numbers of phagocytic histiocytes filled with lipoid, blood pigments, or both. If associated with capillaries and phagocytes, it is generally called fibrous xanthoma



FIG. 13. *Fibrosarcoma of the mesentery of the jejunum. This was in infiltrating growth, 7.5 cm. in diameter, that had deformed the intestinal wall to which it was closely adherent. There had been no recurrence of symptoms eighty-two months after resection.*

or sclerosing hemangioma and is always benign. It has a limited growth and never achieves a very large size. If, on the other hand, it is purely fibrous it may display continuous progressive infiltrative growth. The smaller tumors of this variety do not recur after excision but the larger ones may do so and for all practical purposes behave like locally malignant neoplasms. The smaller ones with limited growth are generally called fibromas while the larger ones that show progressive growth are called fibrosarcomas. It is not possible to distinguish the two histologically so that, as Wilson has pointed out, it is necessary to depend upon size and progressive growth for this purpose.

In the deeper tissues similar fibrous nodules occur but the small benign tumors of limited growth are rarely encountered and it is the larger ones with progressive increase in size that become manifest during life. Out-

standing examples are those that develop in the mesentery and the periosteum. They will receive further attention later in this paper. Here it will be affirmed only that in spite of good differentiation, I classify them as fibrosarcomas because of persistent infiltrative growth.

FIBROSARCOMA

Regional Fibrosarcoma. There is another aspect of these fibrous growths which is outstanding and demands attention. It has already been indicated that fibrous growths developing in the skin itself very seldom metastasize and, except for persistent locally infiltrative growth, rarely show any other evidence of malignancy. This statement does *not* apply to the tumors that develop in scar tissue that may involve skin as well as deeper parts. If true, it would seem to suggest that there is some difference in the tendency of

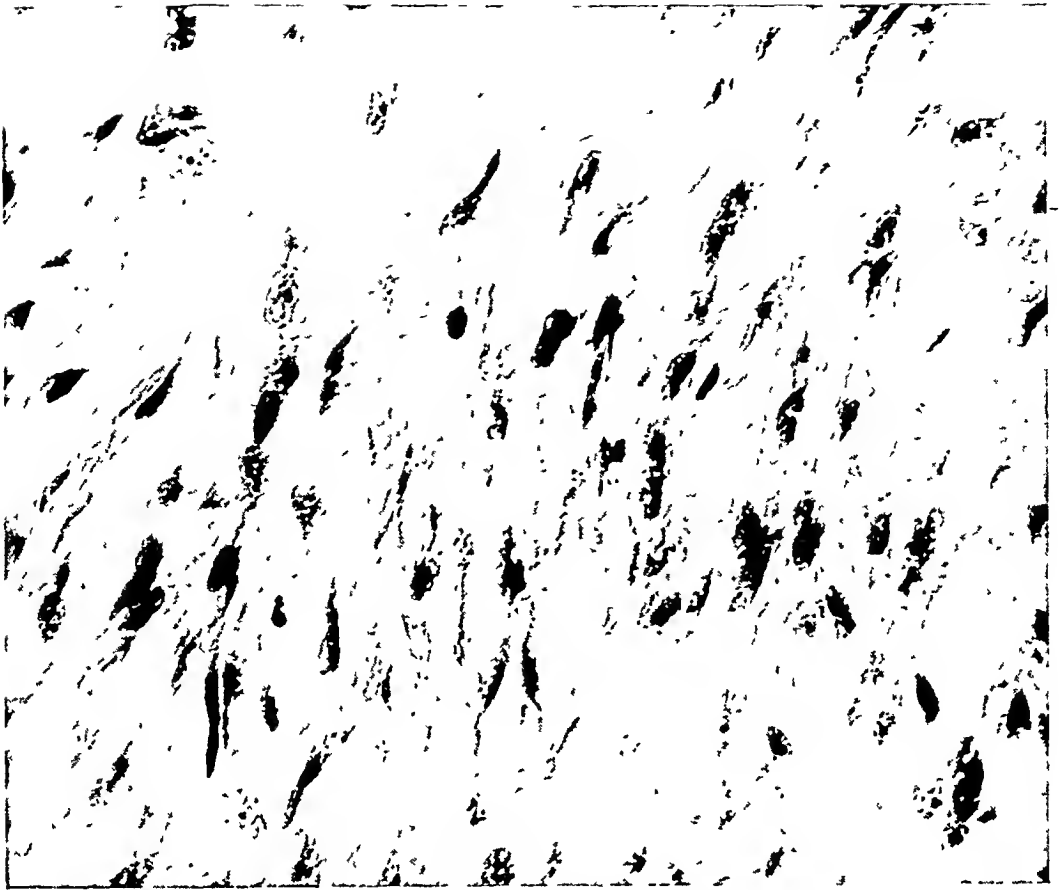


FIG. 14. The same case as Fig. 13. A well-differentiated tumor, composed of fibroblasts and many intercellular connective-tissue fibers. $\times 470$.

certain parts of the body to develop malignant fibrosarcomas when compared with other parts. It is difficult to accumulate follow-up records of such tumors in sufficient numbers for a proper comparison, but the matter is of sufficient importance for prognosis and treatment to warrant a review of what data can be adduced. The alimentary tract will first be considered.

ALIMENTARY TRACT. Before reviewing this, it seems important to repeat the caution that some cases reported as fibrosarcoma, neurogenic sarcoma, and spindle-cell sarcoma may actually be smooth-muscle tumors that, in the *gastrointestinal tract*, certainly are far more common than malignant connective-tissue tumors.¹⁸⁸ For the stomach D'Aunoy and Zoeller state that 7 per cent of 335 sarcomas are fibrosarcomas; Geschickter⁷² reported 10 neurogenic sarcomas in the gastrointestinal tract from the Johns Hopkins Hospital ma-

terial, 3 of which were in the stomach, 3 in the small intestine and 4 in the rectum: Counsellor and Collins found 7 fibrosarcomas among 135 gastric sarcomas at the Mayo Clinic; other gastric cases have been reported by the Cook County Hospital and by Freeman: a possible duodenal case is described by Laroque and Shifflett: jejunal cases by Leriche and Brun and by Matsubara, and a possible case in Meckel's diverticulum by Faust and Walters. In the Columbia University material there are no cases recorded from the Presbyterian Hospital: only one gastric case is included coming from a source outside the hospital, about which no clinical information is available. No conclusions can be reached about prognosis and malignancy from such unsatisfactory data.

When one considers the *mesentery*, *omentum*, and *retroperitoneal region* some peculiar facts come to light. Fibrous growths are con-

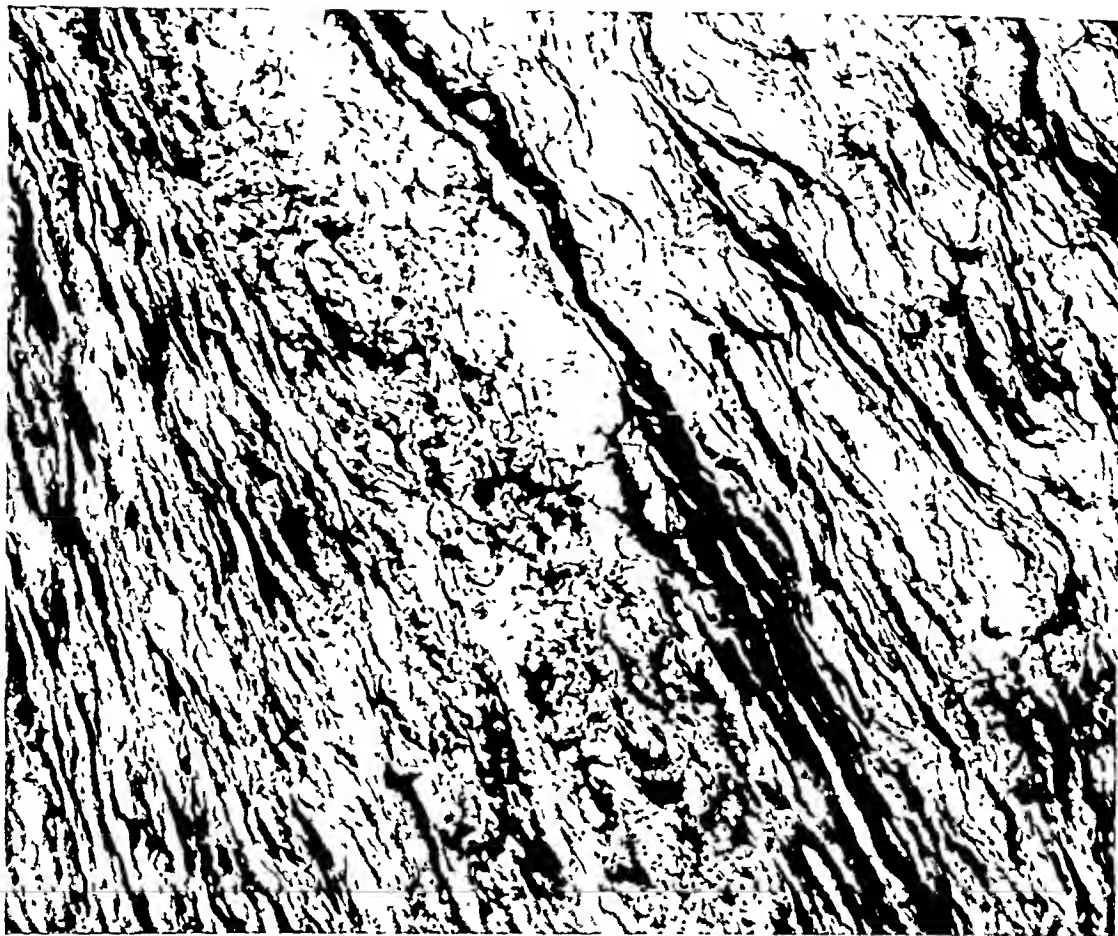


FIG. 15. *The same case as Figs. 13 and 14. Laidlaw silver reticulin stain; this shows the large number of mated reticulin fibers. $\times 470$.*

siderably more frequent in the mesentery than in the retroperitoneum proper. For instance, in the Columbia University series there are six cases of fibrosarcoma in the mesentery and only one in the retroperitoneum. The reverse of this is true for other varieties of tumor. All of the cases in the present series were well differentiated. All six of the mesenteric tumors necessitated resection of the adjacent small bowel. Two cases were not followed. One had a local reappearance removed after two years, two were well more than five years and one less than five years after operation (Figs. 13, 14, and 15). The retroperitoneal case was not followed. None metastasized. Similar cases involving the mesentery, more often reported in the literature as fibromas than as fibrosarcomas, have been recorded by Bergareche, Bruton, Gordon-Taylor, Matsumoto, Micca, Poulson, Summers, Suzuki, and Weaver. Micca's patient had a local recurrence with the formation of tum

a fecal fistula and death after seven months. One of Matsumoto's two cases was found at the autopsy of a 51-year-old male. It was attached to the mesentery and bladder, weighed 3240 gm., and had metastases in the liver. This is the only case with metastases and it is not certainly a fibrosarcoma, since it is reported only as a spindle-cell sarcoma. No fibrosarcomas are included in Jáki's report of six malignant mesenteric tumors. Rankin and Major's compilation of mesenteric tumors from the Mayo Clinic includes eight sarcomas but their types are not revealed. Although most cases are found in adults, Bruton recorded a congenital case and other examples in children are described by Summers, Suzuki, and by Weaver.

Omental cases have been described by Lawler, Fox and Cohen, and by Mirizzi. Strauss found one fibrosarcoma of the omen-

had a local recurrence with the formation of tum among 14,455 autopsies; Ransom and

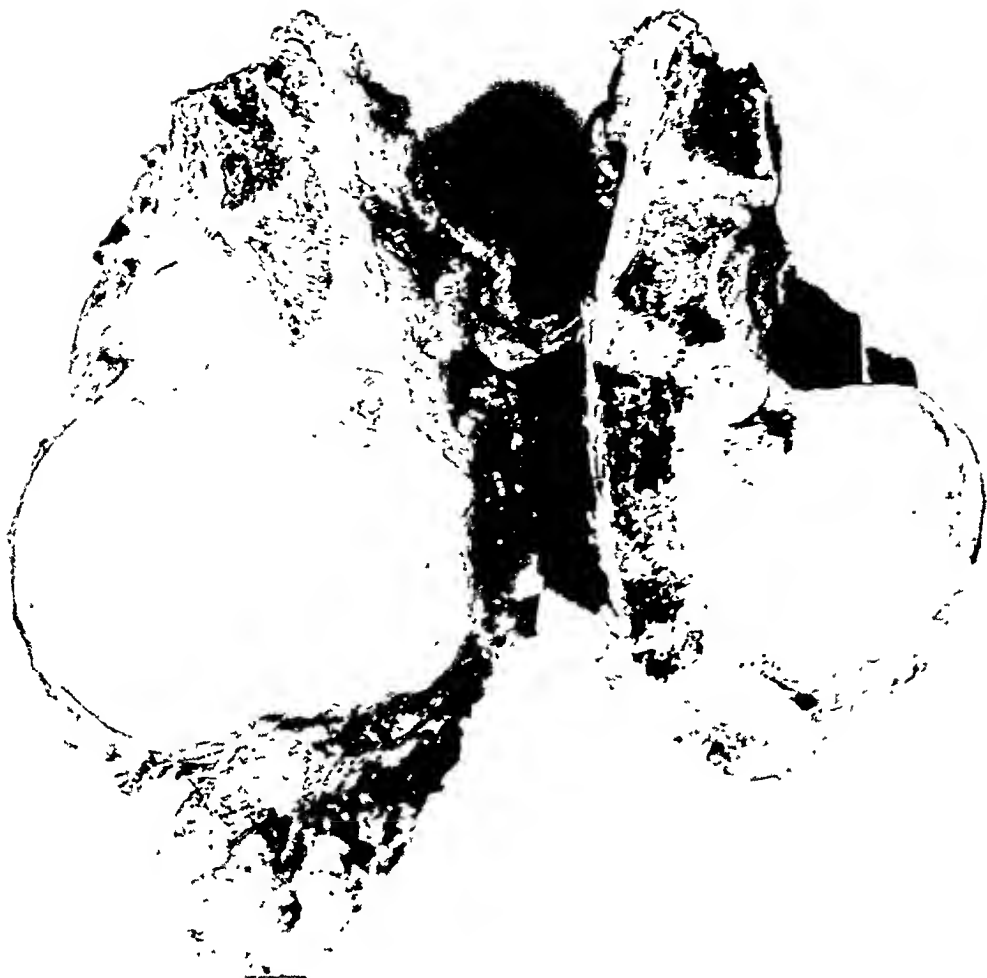


FIG. 16. *Fibrosarcoma of the periosteum of the coccyx in a forty-one-year-old female. It measured 5 × 4 × 3 cm. and had pressed forward to indent the rectum. It had not recurred sixteen years after resection.*

Samson recorded thirteen fibrosarcomas among seventy-five malignant tumors of the omentum reported in the literature. Cases called spindle-cell sarcoma have been described by Greig and by Joachimovits. A peritoneal case forming multiple nodules was recorded by Watanabe. This may, however, have been a mesothelioma masquerading as a fibrosarcoma. The possibility of this phenomenon has been discussed by Stout and Murray. *Retroperitoneal* tumors in the pararenal region are reported by Arenas, by Howard and Suby, by LeGac, and by MacLeod. Papin and Mahon found a large one weighing 12 Kg. springing from the base of the broad ligament. Other cases have been described by Phillips, by Rasmussen, by Smith

and Armstrong and two by Warren and Sommer. Eight so-called retroperitoneal fibrosarcomas were reported by McNamara, Smith and Boswell but not one of them is above suspicion of being leiomyosarcoma, liposarcoma, or something else.

Liver cases have been recorded by Hammer and by Shallow and Wagner although the latter is questionable. Gaetani found one in the *gallbladder*. From this review it seems very probable to me that pure fibroblastic tumors of the mesentery, omentum, and retroperitoneal tissues are uncommon and in the great majority of instances well differentiated and nonmetastasizing. It appears wiser to classify them as fibrosarcomas rather than fibromas because they display progressive in-

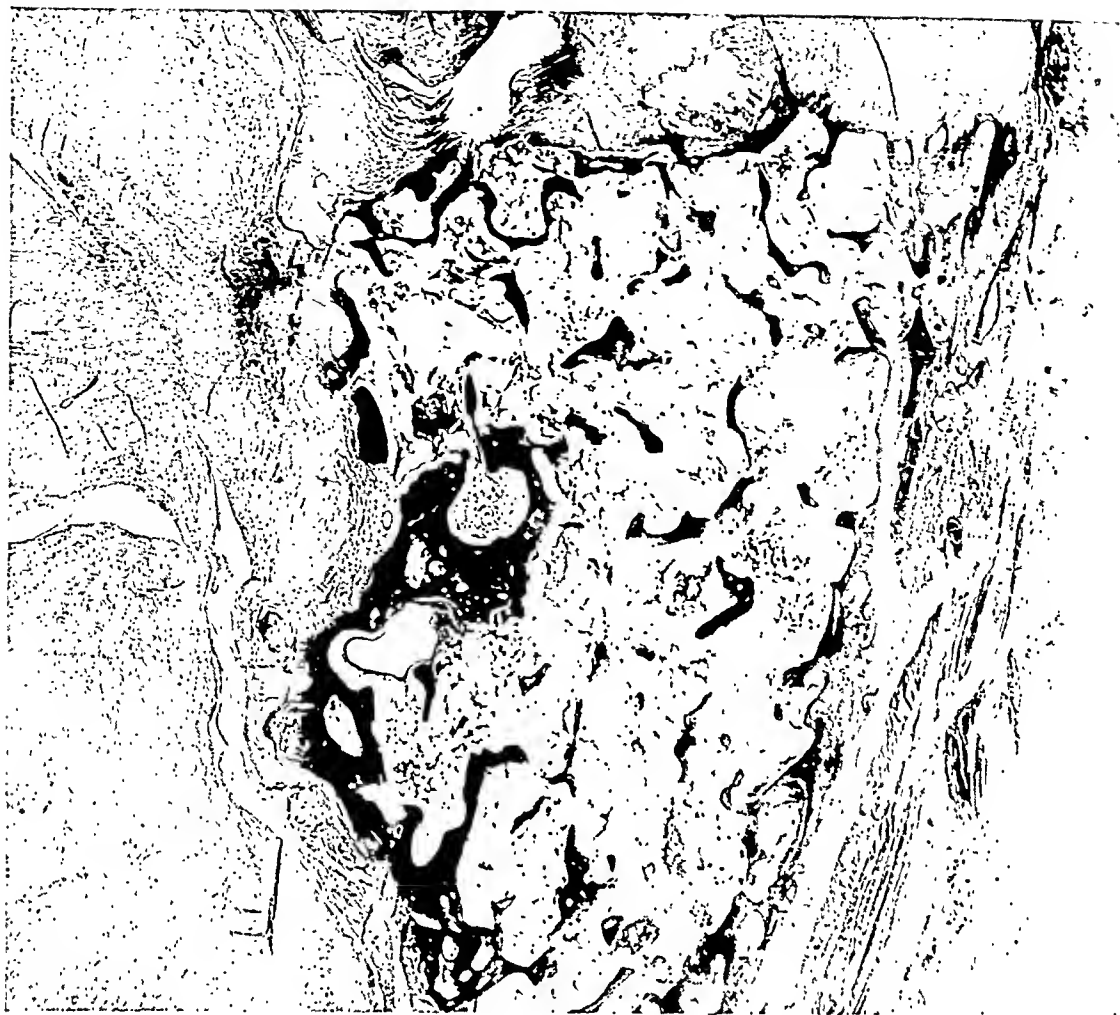


FIG. 17. The same case as Fig. 16. Low-power photomicrograph of the well-differentiated tumor shows erosion and limited invasion of a coccygeal segment.

filtrative growth necessitating radical excision if local recurrence is to be avoided. Metastasis must be an exceedingly uncommon event.

Most of the *mammary-gland* fibrosarcomas represent growths affecting the stroma of intracanalicular fibroadenomas. These have the microscopic appearance of well-differentiated fibrosarcoma and cause great, sometimes gigantic, enlargement of the tumor. Such growths have been called cystosarcoma phyllodes. They have been described extensively by Fox, Isidore, Sailer, and Hill and Stout. The cases of cystosarcoma phyllodes have not been included in this report. In the great majority of instances they are cured by excision of the tumor or mastectomy, although rare cases of recurrence and even metastasis have been reported. Pure fibrosarcomas in the mammary gland unrelated to cystosar-

coma phyllodes occasionally develop. There are only five such cases in the Columbia University collection and the information about them is meager. One, treated by radical mastectomy, was well nine-and-one-half years later. One reappeared immediately after incomplete excision; the ultimate result is unknown. A third patient died at an unstated interval after mastectomy and at autopsy a small metastasis was found in the heart muscle. No information at all is available about the other two cases which were treated by simple mastectomy. When the compilations of the authors above referred to are perused it becomes quite apparent that a number of the cases called fibrosarcoma which metastasized do not belong in the category of fibrosarcomas used in the restricted sense but are rhabdomyosarcomas, liposarcomas or mixed

mesodermal tumors (mesenchymomas). If these cases are excluded the number of metastasizing fibrosarcomas is greatly reduced and

this phenomenon is probably quite infrequent.

The tumors which are attached to the *periosteum* and so seem to spring from it are

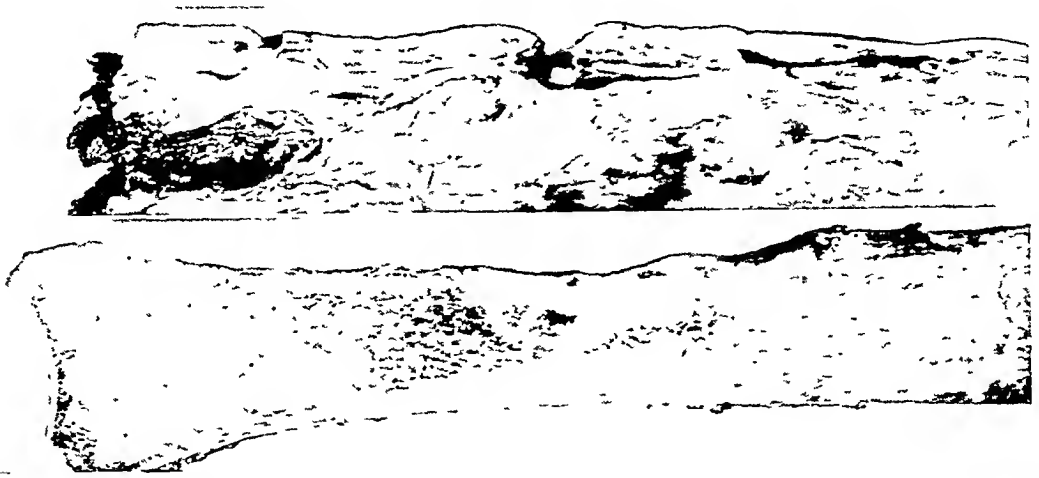


FIG. 18. Above: fibrosarcoma of the periosteum of the tibia of a sixty-four-year-old male with extensive diffuse infiltrative growth in the overlying soft parts. Below: invasion of the tibia.

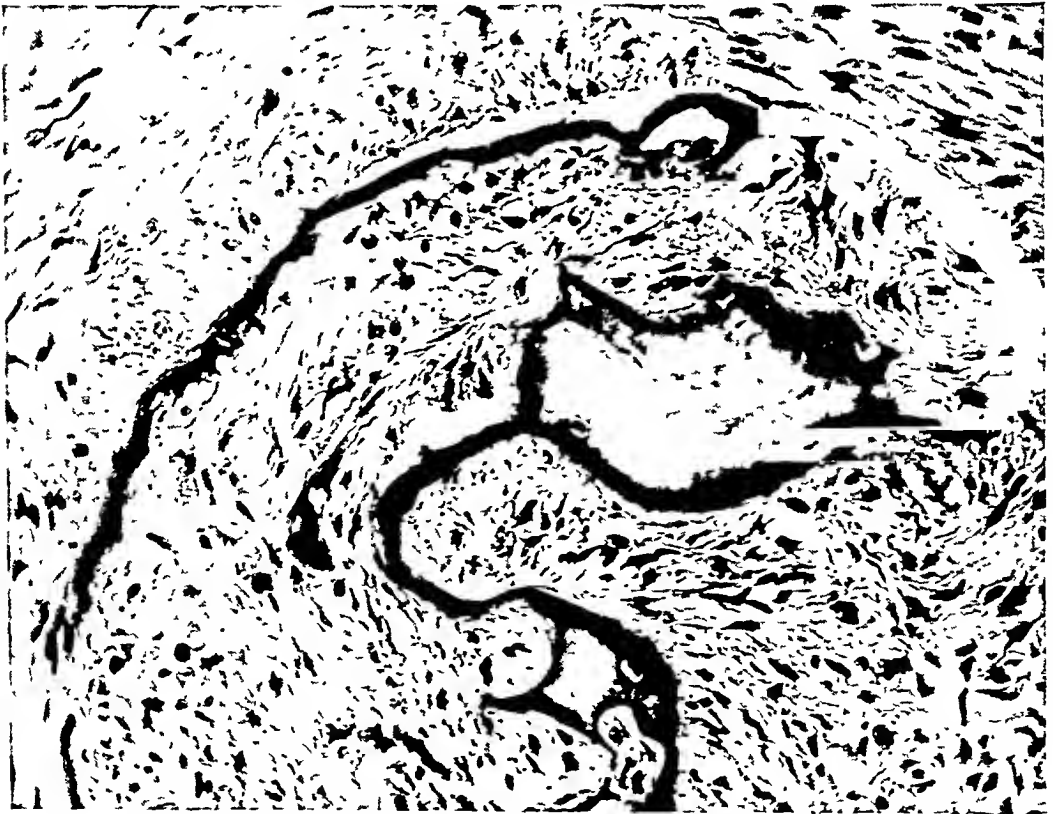


FIG. 19. Same case as Fig. 18. Photomicrograph showing the peculiar effect upon a bone trabecula which has been hollowed out by the infiltrative growth. There are a great many intercellular fibers found but the cells vary somewhat in relative size and show some anaplasia. H. and E. stain. ($\times 250$.)

of considerable interest. There were thirteen of them in the Columbia University series and the bones involved were: scapula, five; mandible, three; ischium-sacrum, one; coccyx, one; femur, one; tibia, one; humerus, one (Figs. 16 and 17). This predilection for bones other than the long bones is borne out by published reports. Other scapula cases are reported by Doub, Soares Hungria, and Strode and Fennel; Van Neck has described a case springing from the periosteum of the astragalus: Geschickter^{70, 71} does not believe there are endosteal fibrosarcomas but only those that start in the periosteum or parosteal tissues. According to him, the periosteal cases are relatively benign and seldom metastasize; the parosteal cases invade the bone secondarily and are much more malignant. I agree with these statements and believe that all of the cases of apparent endosteal fibrosarcoma of bone are either osteogenic sarcomas or chondrosarcomas without convincing evi-

dences of differentiation. Only one of the thirteen Columbia University periosteal cases is known to have metastasized. This was in a 64-year-old male with a deep tumor of the leg, which was quite possibly parosteal to the tibia rather than primarily periosteal. Much of it was well differentiated, forming a great deal of collagen, but some areas had a more malignant aspect with cellular anaplasia and many mitoses. After one year of growth an incomplete excision was done followed by amputation through the thigh; death with lung metastases ensued seventeen months after the first operation (Figs. 18, 19, and 20). Two other patients died and one was last seen alive with persisting tumor, but this was because either curative operation was refused or the position of the tumor or age of the patient prevented curative treatment. Four patients were without signs of tumor more than five years (two of these more than ten years) after treatment. Of the cases re-

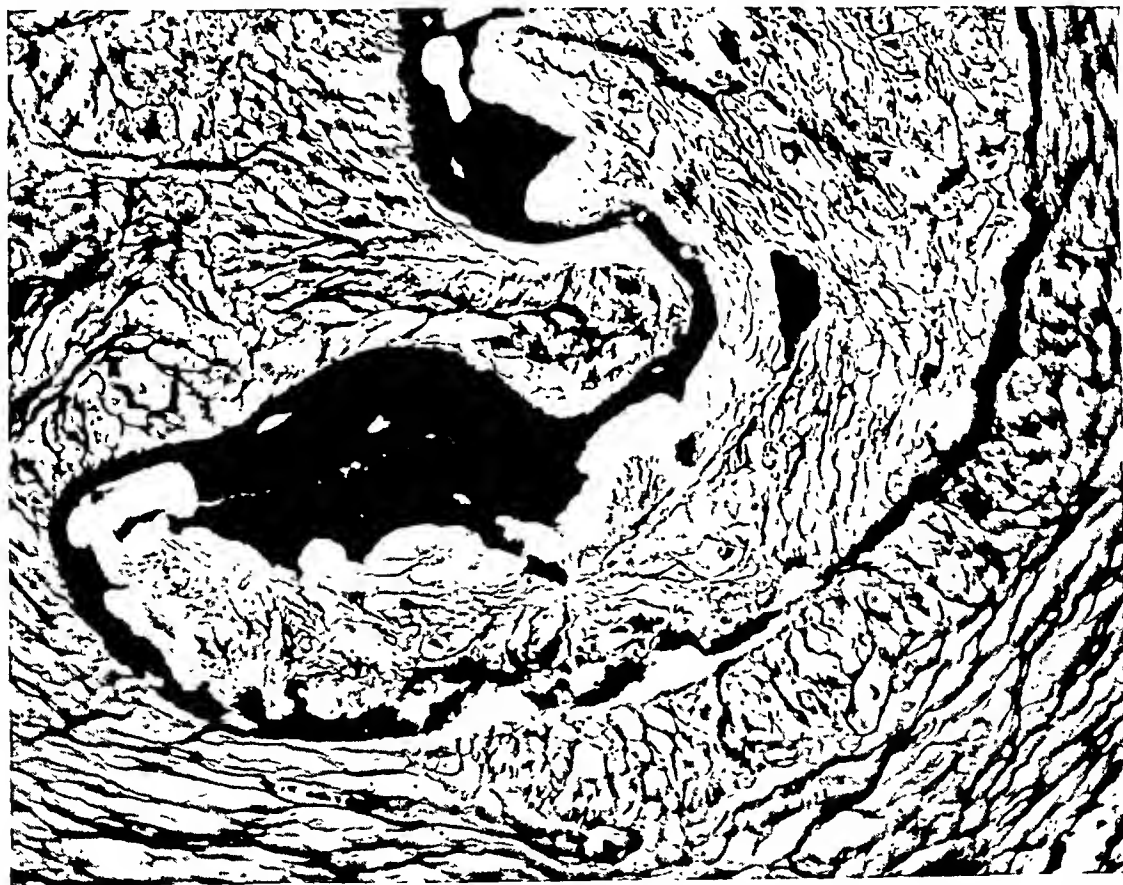


FIG. 20. Same case as Figs. 18 and 19. Laidlaw silver reticulin stain showing the arrangement of the reticulin fibers formed by the tumor which are wrapped around each cell ($\times 250$.)

ported in the literature almost all that metastasized were probably either parosteal tumors or else undifferentiated osteogenic sarcomas masquerading as spindle-cell fibrosarcomatous tumors.^{24, 30, 103, 105, 109, 195} Incidentally, possible fibrosarcomas attached to *joint* capsules are exceedingly rare. Wehner described what he called a fibroma that grew below the patella for fifteen years following a tear of the patellar tendon, and in their list of primary joint tumors Razemon and Bizard mention spindle-cell sarcoma. Whether or not this includes fibrosarcoma remains uncertain.

CENTRAL NERVOUS SYSTEM. Baker and Adams have described a fibrosarcoma in the right frontal lobe and refer to four others all in the frontal or temporal lobes. They suggest that these probably originate from the adventitial connective tissue or from perivascular sheaths of cells extending down from the leptomeninges. Russell and Sachs have described four malignant meningeal cases, three of which metastasized and the other invaded blood vessels. They called them arachnoidal fibrosarcomas. Gardner and Turner describe fibroblastic tumors of the choroid plexus of the lateral ventricles. T. Fahr described a diffusely growing spindle-cell tumor involving the leptomeninges that covered the left parietal and temporal lobes and the entire spinal cord.

A *suprarenal* case with many metastases is reported by Cran; a doubtful *thyroid* case by Moulouquet.

GENITOURINARY SYSTEM. In the *kidney*, cases spring from the capsule,⁸³ from the pararenal tissues;¹²¹ from the pelvis;¹¹⁵ and occasionally from the kidney itself.^{14, 139, 163, 189} Monserrat and Galvez found one in the *testis* proper; O'Brien, and Halpert and Thompson reported cases in the *epididymis*; Chwalla and Donati each described a fibrosarcoma of the *tunica vaginalis*, and Sordina one in the *spermatic cord*. Cases involving various parts of the *penis* have been recorded by Bailey, Evans, Hval, and by Nakazawa. Two *prostate* cases are cited by Warren and Sommer. A *vulvar* growth is reported by Nelson and a *vaginal* one by Warren and Som-

mer. Most of the *ovarian* cases are probably either simple fibromas or theca-cell tumors. None of the cases called fibrosarcoma in the following four papers is thoroughly convincing.^{10, 31, 33, 39}

Lung cases have been described by Ball, Johns and Sharpe, Lutembacker, and by Scheidegger. Other cases reputed to have arisen from the *pleura* are reported by Klemperer and Rabin, Lyssunkin, and by MacMahon and Mallory. One must repeat here what has already been said about apparent fibrosarcomas of the peritoneum. As pointed out by Stout and Murray, some of these may be mesotheliomas of the *pleura* masquerading as fibrosarcomas. *Mediastinal* cases have been reported by Dolge, Frey, Huguenin and Albot, and by Robins. They must be rare, for Haagensen does not mention fibrosarcoma in his review of mediastinal tumors.

Sporadic cases have also been reported in the *upper respiratory* and *alimentary tracts*. Three examples in the *lower lip* are mentioned by de Cholnoky. Cases involving the tongue are reported by Dunet; Gougerot, Moure and Eliaseff; Gricouroff; Nicolosi; and Ross. *Tracheal* involvement was noted by Norsk, by Richards and Dietrich, by Watson-Williams, and by Weinberg. *Laryngeal* tumors have been reported by Lacaille and by Texier; and a fibrosarcoma springing from the cricoid cartilage that pressed on the larynx and invaded the neck, by Glynn. A retronsopharyngeal tumor was described by Tartakowsky; fibrosarcomas of the *nasopharynx* itself by Bahgat, by Barth, and by Portmann and Davis. Bérard and Sargnon's case involved the nasopharynx, antrum, and orbit, but after extensive excision and radium treatment the patient remained well for twenty years. A Cabot case started in the forehead and invaded the orbit, the antrum, and other sinuses, eventually terminating fatally. Forero described one which started in the *nasal cavity* and Portela another that invaded the sinuses extensively, ending in meningitis and death of the patient. *Orbital* fibrosarcomas have been recorded by Cunningham, by Dey, and by Fouassier; and Morgan described one that involved a lower eyelid.

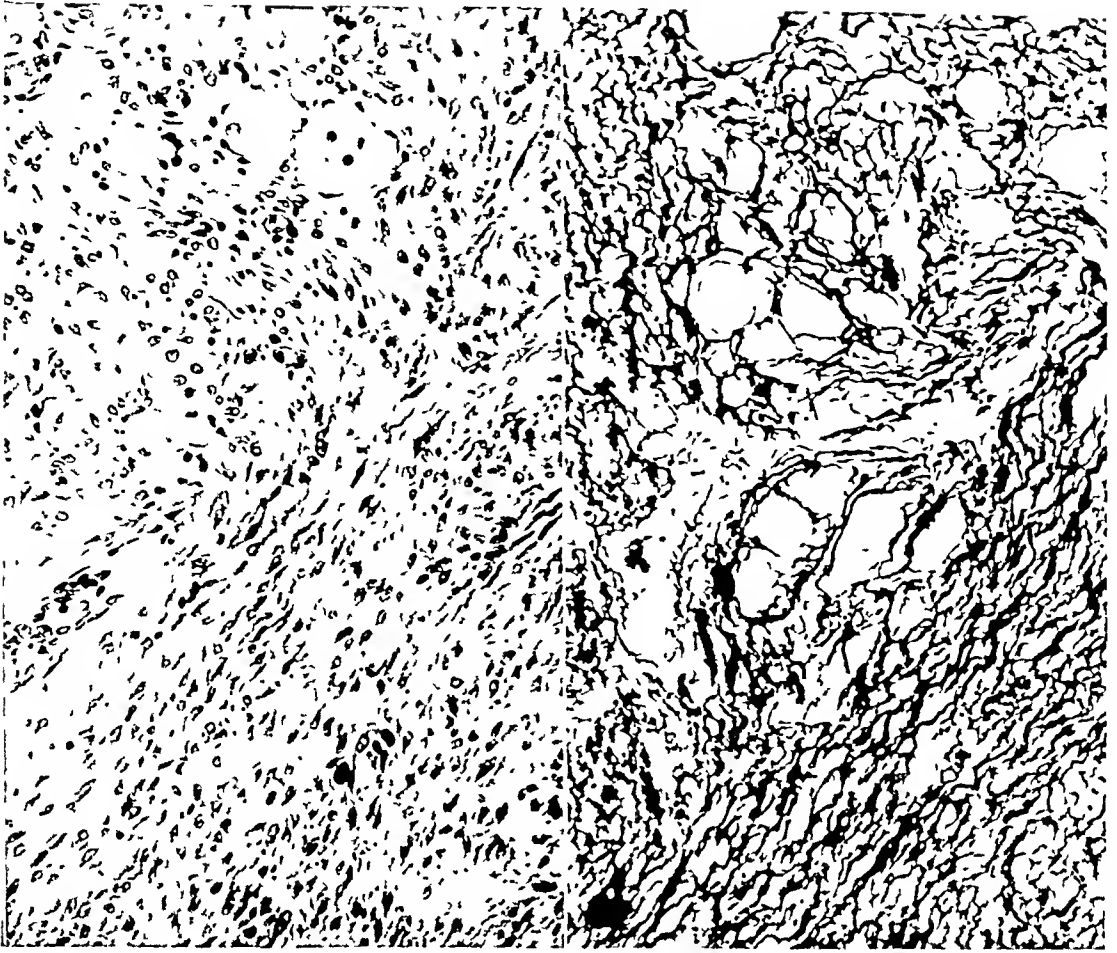


FIG. 21. *Fibrosarcoma of the back muscles which grew for two years in a 29-year-old colored male to reach a diameter of 10 cm. No recurrence 4 years after resection with surrounding muscles. The photomicrograph shows the sinuous curves of the well-differentiated fibrosarcoma as the cords of cells and fibers interlace and infiltrate between transected muscle fibers. H. and E. stain left, and Laidlaw silver reticulin stain at right showing the reticulin fibers wrapped around each cell ($\times 135$.)*

they emphasize that the greater number of the malignant cases are located in the thigh which location consequently entails a high fatality rate.

Tables 1, 2 and 3 summarize the results of treatment of the Columbia University series. With the skin and desmoid tumors excluded, there remain 144 cases of fibrosarcoma of the soft parts of which 107 were followed. Because of the known long duration of these tumors it has seemed proper to date survivals from the reputed recognition rather than from the day of treatment because this gives a better idea of their relative lack of malignancy. It can be seen at once that in spite of a 60 per cent recurrence rate only 8 per cent are known to have metastasized and

that death ensued in only 20 per cent as a result of tumor growth. The figures for fibrosarcomas of all parts are comparable. Moreover, although the death and metastases rates for the lower extremity are slightly higher than for other areas, the difference is far from striking and the same observation applies to the tumors arising in the muscles, tendons, and tendon sheaths. This gives a very different idea of the relative malignancy of the fibrosarcoma than that gained from the previously quoted reports and, of course, requires some explanation. I believe that this is to be found in the much more searching investigation and analysis to which the Columbia University group of sarcomas has been subjected, for this has served to remove

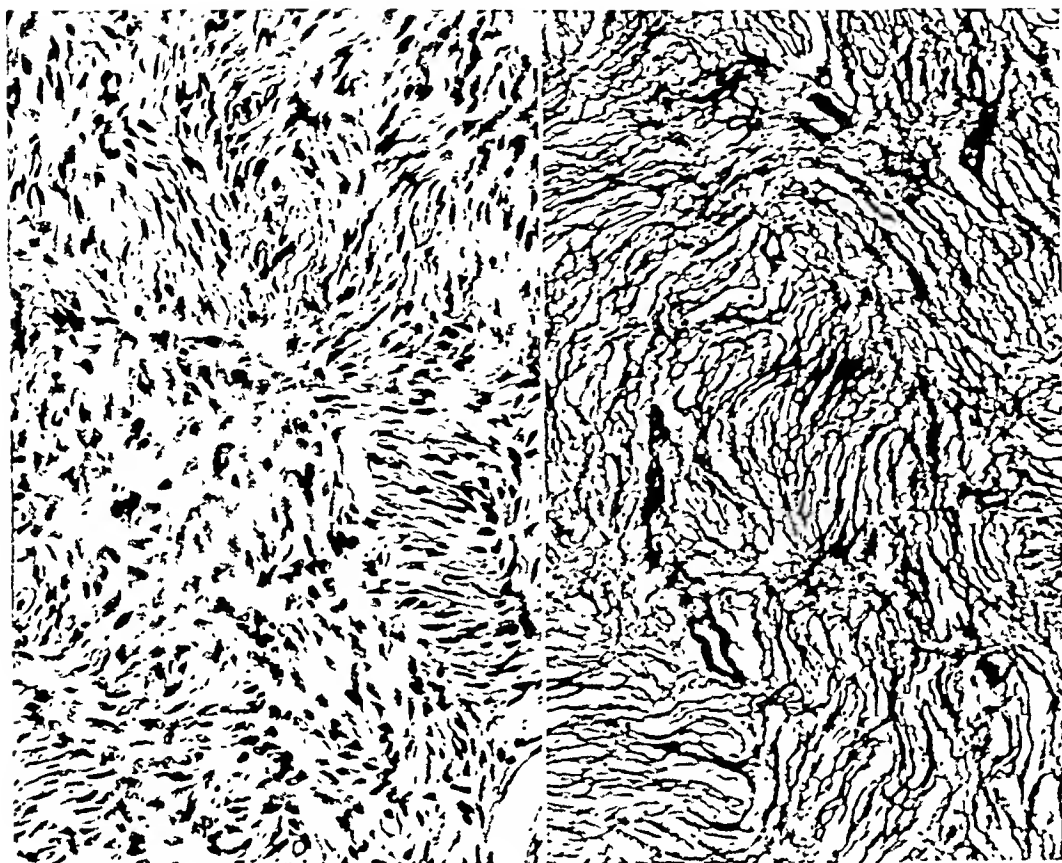


FIG. 22. *Fibrosarcoma of the subcutaneous tissue of the deltoid region of a fifty-four-year-old male, 4 cm. in diameter. There was no recurrence eight months after excision. This is one of the characteristic appearances of the well-differentiated fibrosarcomas in which the bundles of cells and fibers bend sharply at right angles when they meet. H. and E. stain at the left; Laidlaw silver reticulin stain at the right. $\times 195$.*

from the category of fibrosarcoma many malignant tumors that I believe should be assigned to other diagnoses. It will be well to review these although some of them have already been mentioned. I do not recognize the diagnosis myxosarcoma; in my opinion such tumors are either myxomas, liposarcomas, mesenchymomas, or rarely areas of undifferentiated mesenchyme in such tumors as rhabdomyosarcomas. It is indeed uncommon for one of these areas to be found in the fibrosarcoma. The fact that fibrosarcoma-like areas are always found in synovial sarcoma, and sometimes in liposarcoma, Kaposi's disease, leiomyosarcoma, rhabdomyosarcoma, and hemangiopericytoma, means that a casual examination of one tumor area without differential stains may lead one to mistake

any of these tumors for fibrosarcoma. The uncommon malignant schwannomas which are spindle-cell tumors and easily mistaken for fibrosarcomas should also be excluded from the fibrosarcoma group because of their cellular derivation.

Histopathological Criteria of Fibrosarcoma. What then are the criteria by which a fibrosarcoma may be recognized? These are tumors composed of fibroblasts—cells the primary function of which is to form connective-tissue fibers. These fibers are called collagen when they are thick and are stained a reddish hue after impregnation with silver which has been toned with gold chloride. If they are very slender they are blackened by silver. In this country such blackened fibers are usually referred to as reticulum. This is perhaps un-

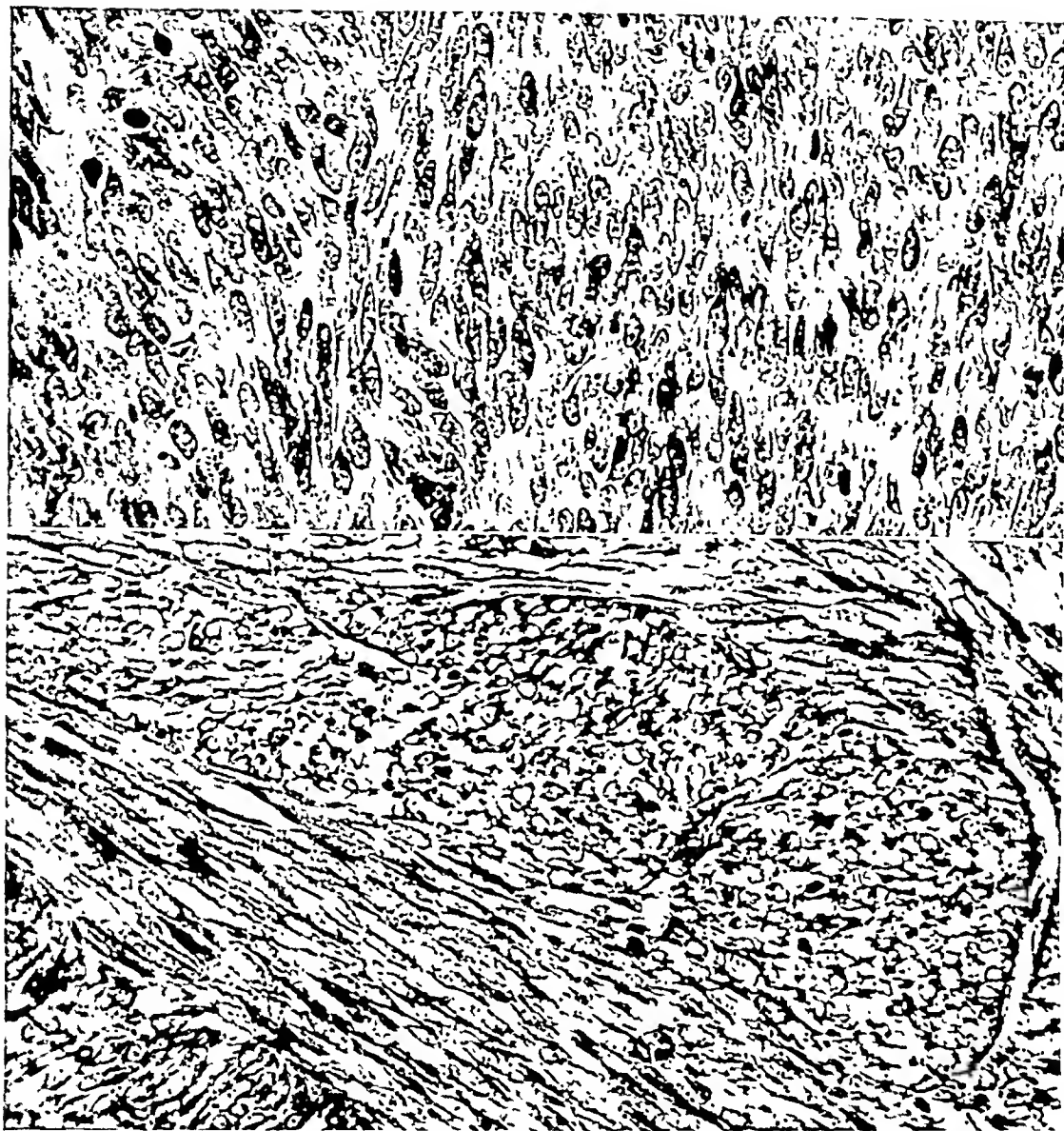


FIG. 23. *Above: fibrosarcoma of the muscles of the dorsum of the foot which grew in a twenty-eight-year-old man and recurred after excision, finally necessitating a Syme amputation. There was no recurrence nine years after the first excision and seven years after amputation. This is an incompletely differentiated tumor showing some degree of anaplasia and frequent mitosis. Below: Laidlaw silver reticulin stain shows many delicate reticulin fibers wrapped around each cell and the sinuous interweaving of the bundles. $\times 470$.*

fortunate because by its use there is danger of confusing these fibrils with many cellular reticula of quite different composition which are found in the body. I prefer to follow Nageotte, the great French master of the earlier study of collagen and call the silver-blackened fibers "reticulin." By so doing there is no possibility of error and confusion.¹⁴⁸ The fibroblastic tumor, then, is primarily characterized by the formation of collagen and ret-

iculin fibers. These fibers are wrapped all around the cells as has been pointed out by Bayer, Dublin, Grynfeldt and others instead of forming long wiry straight fibers of reticulin such as are more apt to be found in the neurilemoma, the malignant schwannoma, and the leiomyosarcoma. This statement applies only to the relatively well-differentiated fibrosarcomas, for the poorly differentiated tumors may have some cells not com-

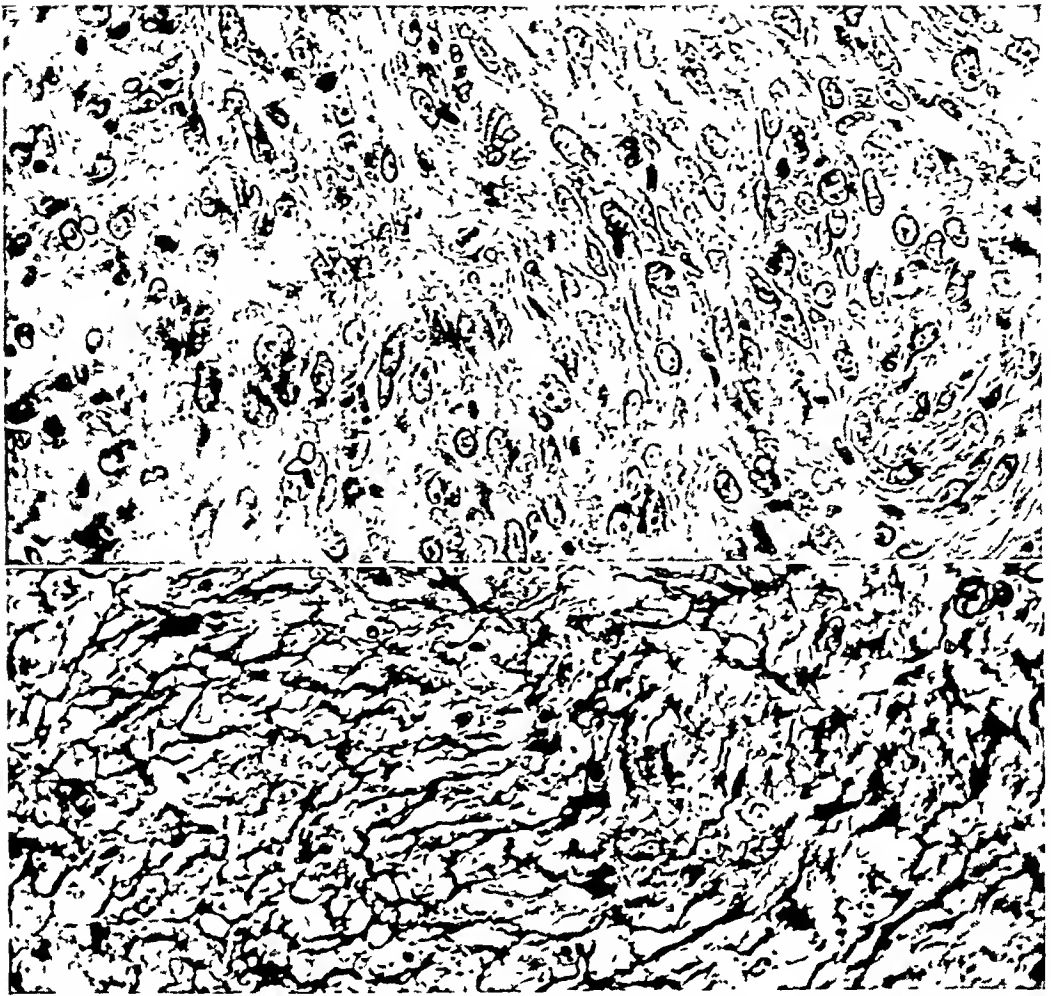


FIG. 24. Above: fibrosarcoma of deep tissues in the arm of an 80-year-old woman. Three weeks after discovery it was 8 cm. in diameter. Biopsy only without treatment. Death after eight months of undetermined cause. Marked anaplasia with variation in cell size and frequent and sometimes bizarre mitoses. Below: a Laidlaw stain showing delicate reticulin fibers incompletely surrounding most of the cells. ($\times 390$.)

pletely surrounded by fibers. Tureen and Seelig believe that the variety and appearance of the connective-tissue fibers of the locus of origin influence the kind of fibers which will be formed in a given tumor. There may be something in this idea but it is exceedingly difficult to prove. Although the great majority of fibrosarcomas are furnished with plenty of reticulin and usually with collagen fibers, there are some in which the tumor cells form relatively little reticulin and no collagen fibers. These have the cells closely placed and demand the closest examination to determine whether or not they are fibrosarcomas, sarcomas of some other vari-

ety, or malignant schwannomas. Only if an exhaustive examination fails to show any other differentiation and their other features correspond with fibroblastic tumors is it safe to place them in the category of fibrosarcoma.

The fibrosarcoma has its cells and fibers arranged in interlaced bands. This type of growth characterizes thick scar tissue: it is seen in the keloid, in the fibroma, and in the desmoid. Moreover, scar tissue, keloids, and fibromas are not contained within a proper capsule; rather the cells and fibers always interdigitate to some degree with the surrounding tissue and this also is true of the

fibrosarcoma. In the differentiated fibrosarcoma that is well supplied with fibers, the interlacing arrangement occurs in two different forms. In the more common one the bundles or cords of spindle-shaped cells and fibers are sinuously intertwined or interlaced; that is, their curves are slight and gentle (Fig. 21). In a few cases the cords tend to be bent abruptly and almost at right angles before suddenly pursuing their course in an entirely different plane. This gives the tumor in cut section various focal points where it appears as if some violent distortion had taken place, somewhat reminiscent of the appearance of a photograph of a spiral nebula (Fig. 22). This arrangement is found also in some skin fibromas and in fibrous xanthomas (so-called sclerosing hemangiomas). It has even been suggested that such growths are derived from nerves without, in my estimation, any proof at all.

The cell of the fibrosarcoma is almost invariably spindle shaped. Its nucleus conforms to the shape of the cell and is elongated with almost pointed ends. The cytoplasm is frequently fibrillated but the fibrils are not of recognizable collagen or reticulin, since these substances are formed outside of the cell. Nor, of course, are they myofibrils. The cytoplasm is never granular and if any vacuoles are found they are not secretional but represent degenerative phenomena, for these cells do not secrete lipoid or glycogen. Since many fibrosarcomas grow slowly, mitoses are commonly very difficult to find. It is in the small group of tumors that grow rapidly and

Differentiation. Many authors have classified the fibrosarcomas into the differentiated forms with many fibers and the more cellular forms with few fibers. Broders, Hargrave, and Meyerding use the terms fibrogenic and cellular spindle-cell sarcoma. Grynfeldt divides them into fibrillogenic and nonfibrillogenic forms. Quick and Cutler, Stewart and Copeland, Warren and Sommer, and others use the term "neurogenic sarcoma" for the more cellular forms, and Foot terms them neurogenous sarcomas. In the Columbia University series the cases have been divided into two groups depending upon the degree of differentiation. If the cells are relatively uniform, without much hyperchromatism, with well-developed collagen and/or reticulin fibers and, most important of all, relatively few or no mitoses, the tumor is considered well differentiated. (Figs. 21, 22.) But, if the cells are closely packed, with no or few collagen and only delicate reticulin fibers, if there is some hyperchromatism and perhaps some variation in cell size, and if the mitoses are frequent, the tumor is classified as poorly differentiated (Figs. 23 and 24). The tumor is called poorly differentiated if only part of it shows this anaplasia. This very rarely happens but was outstanding in one periosteal case in the leg that, in spite of being densely fibrous with much collagen formation, showed areas of great cellular activity with cellular irregularity and frequent mitosis. This tumor invaded the tibia and metastasized to the lungs (see Figs. 18, 19, 20).

Etiology. The anatomical distribution of

TABLE 4
AGE AT ONSET OF FIBROSARCOMA

Years	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
Cases	11	17	49	42	39	27	7	4	4

fail to form many fibers that mitoses are most easily found and in relatively greater number. In my experience, bizarre giant cells either with a single or with multiple nuclei are exceedingly uncommon—if they appear in considerable numbers the tumor generally proves to be not a fibrosarcoma but either a liposarcoma, rhabdomyosarcoma, or leiomyosarcoma.

the fibrosarcoma has been displayed in the preceding pages. It remains only to record a few other facts. Table 4 shows that the tumor can appear at any age from birth to old age. The sex distribution in the Columbia University group (Table I) shows no variation, for, if the twelve females with desmoid tumors be excluded, there are 100 males and 106 females. Twenty-six patients (12 per cent)

were colored—a figure which approximately reflects the proportion of colored patients in the Presbyterian Hospital and Vanderbilt Clinic during the forty-year period. There are no important etiological factors. It has been shown that four tumors developed in tissues damaged by radiation, but this seems insignificant when the huge number of such lesions is considered and when it is compared with the far greater number of radiation epithelial cancers. Similarly there were twelve desmoid tumors that may be presumed to have grown in abdominal-muscle scar tissue and thirty-six other fibrosarcomas that grew in cicatrices of various kinds. Yet when this is compared with the vast number of cicatrices in humans, the association hardly seems significant.

DISCUSSION

This review of the fibroblastic growths seems to show that they can be divided into three categories. The *first* consists of nonneoplastic hyperplasias that are not malignant and apparently, so far as the records show, never lead to the formation of true neoplasms either benign or malignant. In this group are found the so-called pedunculated skin fibromas, true keloids, and progressive myositis fibrosa (hereditary polyfibromatosis).

The *second* group consists of a number of fibrous growths which may or may not be neoplastic. These lesions are almost invariably benign and usually do not reappear after excision but occasionally show persistent growth and may precede the development of true fibrosarcomas. In this category may be included the true fibromas that are usually intradermal but may appear elsewhere, desmoid tumors, the fibrous proliferations in the palmar and plantar fascias and the corpora cavernosa penis, and irradiation fibromatoses.

The *third* group is made up of the true fibrosarcomas, the outstanding feature of which is infiltrative growth. It has been shown that the greater number of these are well differentiated and are characterized either by slow, steady, infiltrative growth often lasting many years or by intermittent growth with long static periods intervening between times of more rapid proliferation.

The majority of fibrosarcomas are contained in this group including most of the cases of dermatofibrosarcoma protuberans,⁹⁷ of progressive dermatofibroma,⁴³ and the rest of the skin fibrosarcomas, most of the mesenteric fibrous tumors, the periosteal tumors, and many of the fibrosarcomas from other parts of the body. While the tumors maintain good differentiation they do not metastasize but, although uncommon, it is possible for them eventually to become less well differentiated and assume the characteristics of the smaller fraction of this third group. This subdivision includes the less well-differentiated tumors characterized by more rapid growth, cellular hyperchromatism, moderate anaplasia, formation of fewer connective-tissue fibers and most important of all a high mitotic rate. Even in this more malignant fraction, the metastatic rate is not high.

It remains only to discuss diagnosis and treatment. Diagnosis should be achieved by biopsy wherever this is possible because treatment and prognosis depend upon the nature and differentiation of the tumor. If it is well differentiated, then the problem is one of local eradication. This has generally been attempted by surgical excision. The high recurrence rate of 60 per cent for the soft-part tumors shows that excision is too often inadequate chiefly because few surgeons appreciate that the fibrosarcoma is a tumor that infiltrates beyond its palpable confines. Although the well-differentiated tumor is not one that threatens life by metastasis, it may do so by local infiltrative growth. The time to cure these tumors with the least damage to the patient is when they are first encountered. Sacrifice of a little extra tissue on all sides and in the depths at this time may save the patient many subsequent operations and perhaps his life.

If the tumor is anaplastic with many mitoses, the case is more urgent and the most radical surgery is indicated. It should include amputation of an extremity if there is any possibility that local excision will fail, for, while metastasis can occur, it is relatively infrequent and the chance of saving life quite good. In all of the cases dealt with in this

paper, metastasis was through the blood stream. It is possible, however, for metastasis to occur through the lymphatics. Examples have been described by Warren and Sommer, and by Hertzler; and a recent case at the Presbyterian Hospital not included in this report had inguinal-node metastasis from a fibrosarcoma of the leg. The occurrence, however, is so uncommon that it seems unnecessary to undertake removal of the regional nodes unless they are involved.

Treatment by radiotherapy has seldom been undertaken because the impression prevails that the fibrosarcoma is exceedingly resistant. This is probably correct in most cases. It was used in thirty-seven of the cases in this series largely as an adjuvant to surgery when the latter failed. In most of these cases it had no appreciable effect but in one, a supraclavicular well-differentiated fibrosarcoma in a 21-year-old male, in whom three attempts at local excision had failed, so much roentgenotherapy was given that not only was the

tumor completely destroyed but the adjacent bone and soft parts as well, necessitating interscapulothoracic amputation. This patient remains well fourteen years after onset and eight-and-a-half years after amputation. In two other patients primary roentgenotherapy after biopsy appears to have had a favorable outcome. One of these patients was a girl 2 years and 8 months old who had a well-differentiated fibrosarcoma springing from the periosteum of the maxilla and filling the antrum. She remains without evidence of tumor eight years and nine months after roentgen-ray therapy. The other is a 28-year-old woman with a well-differentiated fibrosarcoma of the trachea 2.5 cm. below the vocal cord who remains well and with the tumor small and symptomless six years after roentgen therapy. These cases indicate that radiotherapy may have its uses in the treatment of fibrosarcoma. Apparently not all fibrosarcomas are completely resistant neoplasms.

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Lymphangiosarcoma in Postmastectomy Lymphedema

A Report of Six Cases in Elephantiasis Chirurgica

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SURGEON and internist alike are concerned with the complication of the swollen arm when it occurs following radical mastectomy for breast cancer. Unfortunate as it is when it is produced by recurrent disease, it is tragic when it supervenes without clinical evidence of the return of the cancer. When induced by recurrence, palliative measures can be employed until the locus of cancer in a vital organ terminates the problem. When it ensues without the return of the disease, the swollen arm becomes one of the most difficult conditions to treat: witness the number of surgical procedures—some with merit—that have been developed to combat this complication.

The present study is not, however, concerned with the therapeutic phase of this situation. Rather, it deals with a heretofore unrecognized and unreported sequel that ensues in an edematous upper extremity that has developed following radical breast surgery but long after the malignant breast neoplasm has apparently been arrested—namely, the development of a new specific tumor. That similar lesions must have occurred not only in our hospital, but in other clinics, seems certain. That they were erroneously considered as diffusely recurrent, inoperable, cutaneous manifestations of mammary cancer seems probable. Because such patients have doubtless since succumbed to metastases from the second lesion, we are unable now to obtain specimens for study. A case in point may perhaps be seen in the first figure in Hutchins' report on an operation for the prevention of the swollen arm. The condition illustrated appears to be a clinical situation quite compar-

able to the one that we are describing here.

In the early part of the past year a patient was referred for the treatment of multiple cutaneous lesions which had appeared diffusely in the skin of the arm and chest wall of the side subjected to radical mastectomy eight years before the appearance of this second, entirely different lesion. Her recovery from the radical breast surgery had been uncomplicated except that lymphedema had appeared promptly and never regressed. One of these new tumors had been subjected to biopsy and a report of Kaposi's sarcoma made. While we entertained this diagnosis as a possibility, certain features precluded complete acceptance. We then began a careful scrutiny of our clinic patients who had developed brawny edema after radical mastectomy to ascertain if other similar lesions might have supervened. Five months later a specimen of a skin lesion from the posterior surface of the upper arm of one of these was submitted for an opinion. This patient, too, had been operated upon eight years prior to the appearance of the cutaneous lesion. This patient's convalescence following radical mastectomy was likewise uncomplicated except for the immediate appearance of a swollen arm that had persisted for eight years. This lesion was considered a type of angiosarcoma.

There then followed three other patients in fairly close succession. One (case 4) was not observed by us but was carefully described by her referring physicians. The other two were seen in our hospital and subsequently had interscapulothoracic amputations for their lymphangiosarcomas. Having collected five such instances, we then recalled another case of immediate postoperative lymphedema that had followed a radical breast operation. After six years' follow-up, this patient had developed a cutaneous lesion on the anterior sur-

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Received for publication, February 12, 1948.

face of the upper arm; a biopsy of the lesion was reported as Kaposi's disease. In retrospect, this error has been recognized and the case reclassified as lymphangiosarcoma.

CLINICAL DESCRIPTION OF THE SYMPTOM COMPLEX

In all the instances here reported, there has been immediate postmastectomy edema of the arm on the operated side. This occurs without a history of any complication in healing, of postoperative infection, or of known thrombosis. Nor has there been prolonged serous or lymph drainage. The swelling persists and gradually extends from the arm to the forearm and finally to the dorsum of the hand and digits. Sometimes the extremity develops a suffused hue. Initial pain is absent, although increased swelling causes discomfort due to the distention of the skin. The hypertrophy likewise induces a periarthritides and myalgia ascribable not only to the edema *per se*, but also to the pain of tense fasciae produced by the swelling in the muscles. The weight of the hypertrophied extremity results in marked limitation in function, so that the motion of the arm causes pain because of the contraction of unused muscles. This in itself may be a vicious cycle that increases venous and lymphatic obstruction. With the persistence of the brawny edema, minor atrophy of the skin appears; it may or may not be accompanied by attacks of true erysipelas or erysipeloid manifestations. These febrile bouts are incidental, and following them the swelling may diminish slightly owing to the enforced rest of the affected part. These inflammations seem in no way to be tumorigenic. Hyperkeratosis and spontaneous telangiectasia may ensue.

After an interval of years (six in the earliest case) a purplish-red, subdermal, slightly raised, macular or polypoid lesion appears. The primary site is in the skin of the arm or antecubital area. The lesion occurs as a solitary tumor followed by similar satellite areas that sometimes become confluent, forming a larger lesion, or remain as distinct, and later partially bullous, areas. The larger lesions appear almost as papillomatous growths covered

by a shiny, tense, atrophied epithelium that has a tendency to ulcerate and discharge a serous or serosanguinous exudate. They heal spontaneously only to break down again and discharge. As new lesions appear, all stages of imminent ulceration, discharge, and healing can be seen. Once the process is initiated, the discrete nodules continue to grow, and new ones appear on the forearm, dorsum of the hand, and finally the skin of the adjacent thorax.

More particularly, the skin is pachydermatous with pitting edema of varied intensity. The growths are flattened on top, are soft in consistency, and on cut section show a grayish-red, soft central portion in distinction to the purplish-red perimeter. Some of the larger lesions become partially necrotic. With increase in size, the largest lesions become cystic and finally necrose, leaving a central cystic cavity. Necrosis is not complicated by marked hemorrhage; the discharge is serous or slightly bloody. Then with the rapid growth which may ensue, pinkish-red papules appear as myriads of discrete and confluent lesions. These are lighter red and may be observed between linear telangiectases in the keratotic skin.

Clinically, these dermal tumors do not resemble the cutaneous nodules of recurrent mammary cancer. Only remotely may they suggest a similarity to colloid carcinoma. In no instance, however, have the cases reported here shown evidence of local or metastatic carcinoma. They do not appear initially in the operative field nor in the skin of the axilla. For the most part, too, these tumors grow centrifugally as distinguished from recurrent breast cancer which has a tendency to grow centripetally. They are wholly distinct from the initial mammary lesion. The tumors remain aggressive until radical amputation of the arm and shoulder girdle interferes with their growth, or the patient dies from metastasis—in our experience, pulmonary. Roentgen-ray therapy elicited very slight clinical response in two patients (cases 5 and 6).

CLINICAL ABSTRACTS

Case 1 (Private patient of Dr. Frank E. Adair). N.C. was 52 years old when she was

first seen for multiple, cutaneous, purplish-red tumors of the left forearm, arm, and chest wall. The tumor of the skin of the forearm was ulcerating, necrotic, and partially fungating. The other areas showed discrete, partially raised macules and papules.

PAST HISTORY. This was without significance except for the breast operation. The patient had been married at 22 years of age, was never pregnant, and had ceased menstruating at the age of 48.

PRESENT HISTORY. In May, 1938, a small tumor of the left breast was excised. On examination it was reported as "Adenosarcoma, grade III." The patient was then treated by roentgen-ray irradiation for thirty days and after a month's interval had a radical mastectomy. We are unable to find out whether the axillary lymph nodes were involved. Marked brawny edema of the entire left arm appeared one week later, although there were no immediate postoperative complications.

In September, 1946, more than eight years after the mastectomy, the patient fell and

traumatized the left arm and leg. Ecchymotic foci appeared that cleared in all areas except the left forearm where a dark blue nodule persisted. This was followed by similar purplish areas in the skin of the arm where slight trauma was sustained ten days later. From that time on, discrete lesions had continued to appear. Repeated biopsies were done, but it was not until January, 1947, that a report of Kaposi's sarcoma was made. The patient then received 1,500 r to two ports, but the factors of treatment could not be learned. While some clinical improvement was reported, the accompanying illustration shows tumor fungating through heavily irradiated skin (Fig. 1). The chest roentgenogram was reported negative for metastasis, although there was a slight amount of pleural fluid in the left chest as well as slightly increased density of the lung parenchyma.

COURSE. In spite of the widely disseminated disease, an interscapulothoracic amputation was advised. The patient was referred back to her surgeon, and we have been unable



FIGURE 1.

to learn her subsequent history. The pathological diagnosis was lymphangiosarcoma.

Comment. The initial breast tumor may have been in the group of cystosarcoma phylloides. Postoperative brawny edema of the arm had appeared one week postmastectomy and had persisted until the appearance of the second neoplasm. We do not believe that irradiation played any part in the genesis of the tumor of the arm, for there was no evidence of irradiation change in the skin of the chest wall and arm. Nor can trauma be considered an etiological factor.

The second case was observed at an earlier stage of the second lesion when this was still confined, at least in its superficial manifestations, to a solitary area on the skin of the back of the arm.

Case 2. A.K., at the age of 60 years, developed a solitary, painless, fairly bulky tumor of the right breast, that had appeared two months before she was first observed in the Breast Clinic at the Memorial Hospital on January 20, 1939. There was a questionable incident of breast trauma. She had had two children whom she had nursed. Menstruation had continued until the age of 42 years when it was interrupted by a supracervical hysterectomy for fibromyomas.

A radical mastectomy was performed on April 17, 1939, about six weeks after the completion of a cycle of high-voltage roentgen-ray treatments of 1800 r to each of five portals. The examination of the operative specimen yielded a diagnosis of "Plexiform carcinoma of unusual type. *Nodes clear.*" Her convalescence was uneventful and uncomplicated.

PRESENT HISTORY. Immediate swelling of the entire extremity developed which persisted. She remained free of cancer until May, 1947, when a purplish-red tumor appeared in the skin of the posterior arm eight years after the mastectomy. Her family physician referred her to a clinic nearer her home, where the cutaneous lesion was widely excised in the belief that it was breast cancer. A section of the tumor was submitted to our laboratory. The diagnosis was lymphangiosarcoma.

Because of this diagnosis the patient was prevailed upon to return to our clinic. When examined, the entire incision in the arm had broken down and was being prepared for secondary skingrafting. There was no evidence of tumor in the granulating wound nor in the adjacent skin. No further follow-up data are available.

Case 3 (Private patient of Dr. George T. Pack). E.R., when 59 years of age, discovered a tumor in her left breast. She had nursed three children. Her menses ceased when she was 47 years old. A radical mastectomy furnished a specimen which was reported "Infiltrating duct carcinoma, grade III. *Nodes clear.*"

When seen ten years thereafter, examination revealed a well-healed radical mastectomy scar and no evidence of local recurrence or enlarged supraclavicular nodes. The arm was swollen from the shoulder to the wrist and was at least twice the size of the opposite arm. The skin had a definitely yellowish cast, with mottled areas of blue discoloration. Scattered over the arm were multiple tumefactions involving the skin and ranging in size from a few millimeters to over a centimeter in diameter. They all had a deep bluish-purple cast, and were firm and moderately tender when palpated. They seemed to be infiltrative, but the edges were well demarcated. While there were no marked articular changes, there was a flexion deformity at the elbow with a 10° to 20° range of motion, probably due to the edema of the muscles of the arm and forearm. There were no lesions either on the skin of the wrist or on the hand. (Fig. 2.)

OPERATION. An interscapulothoracic amputation was performed on September 17, 1947. The only finding of interest at the operation was very dense scarring about the brachial artery and vein. Again the diagnosis proved to be angiosarcoma.

COURSE. The postoperative convalescence was uneventful, the patient being discharged seven days later. Follow-up at present reveals no local or metastatic disease.

Comment. A biopsy before operation ruled out the possibility of recurrent mammary cancer nor was there evidence of local recurrence in the operative field. The manifestations of the new lesion were primarily in the skin around the elbow joint and forearm. This patient, too, had developed the swollen arm immediately after radical mastectomy. No axillary nodes had been involved by the breast cancer. The second and entirely separate tumor occurred ten years after radical mastectomy.

The fourth case has not been personally observed but we have been supplied with a very complete outline of the history, physical findings, operative procedure and subsequent

course. Sections of the cutaneous lesion have been examined; likewise, later sections from the lungs.

Case 4. R.D. was first observed at the age of 37 years because of a painless mass in the right breast, present for three months, and for which she had received roentgen-ray therapy (dose unknown). She had two children, the second born one year prior to the onset of the breast tumor. During lactation, following the second pregnancy, she had had a bilateral mastitis. A pathological specimen from the radical mastectomy that followed the preoperative irradiation was reported "Scirrhous carcinoma, grade II. *Nodes uninvolved.*"

The swelling of the arm developed one year after operation. It then regressed slightly, only to return. In February, 1941, the patient was re-admitted for excision of axillary scar tissue. The swelling persisted henceforward. In 1943, she was readmitted for a subtotal thyroidectomy for diffuse goiter. In June, 1943, she was again admitted because of an acute lymphangitis of the right arm. Following this infection, the swelling of the arm was even greater and the varicosities that had appeared increased in size and number. In

April, 1947, a "large blood-red cystic area," projecting above the skin surface, appeared in the mid-portion of the medial aspect of the right arm. After that time smaller painless nodules about 1 cm. in diameter occurred in the skin of the forearm. Two nodules about the right elbow were slightly tender. Biopsy was performed three months after the appearance of the first cystic lesion. The section of the tumor, reviewed by a number of pathologists, was considered "a malignant process." It was not recurrent mammary cancer and was diagnosed as lymphangiosarcoma in our laboratory.

The arm was immediately amputated. The patient died five months later of pulmonary metastasis.

Comment. This patient had preoperative roentgen-ray treatment and radical surgery for a breast cancer without axillary involvement. She was the youngest patient of the group to have a mammary neoplasm. While the swollen arm did not develop until one year after operation, it persisted, with only slight regression, after an operation for the removal of axillary scar tissue. It then in-



FIGURE 2.



FIGURE 3.

creased, acute lymphangitis having supervened before the appearance of the lymphangiosarcoma ten years postmastectomy. There was no clinical evidence of local or systemic return of the breast cancer. Amputation of the arm failed to prevent a fatal outcome five months later. The interval between the development of the swollen arm and a second malignant neoplasm was about nine years.

Having observed these four similar cases in a very short space of time, we were alerted for the occurrence of this lesion following the sequel of the swollen arm. The next patient was observed in November, 1947. The cutaneous manifestations were promptly diagnosed as lymphangiosarcoma from the biopsy specimen and interscapulothoracic amputation was performed immediately. More satisfactory anatomical and pathological investigations were made on the operative specimen.

Case 5 (Private patient of Dr. Gordon P. McNeer). M.Q., single, 40 years old at the time of her radical mastectomy, was in her sixty-fifth year when first seen at the Memorial Hospital, twenty-four years after the breast operation. Her arm had swollen immediately after the radical surgery. Her convalescence had been slightly febrile, but otherwise uncomplicated. The breast tumor was reported as a malignant neoplasm, but we were unable to ascertain whether axillary nodes were involved. No postoperative roentgen-ray therapy had been administered to the breast or lymph-drainage areas.

PRESENT HISTORY. One year prior to her recent admission, a painless, discolored lesion, measuring about 4 × 8 cm., appeared over the inner aspect of the left arm. After local treatment for one month, roentgen-ray therapy was given intermittently from June to August; there was some clinical regression. As the treatments were being completed, a small red papule was noted on the posterior aspect of the arm. Similar lesions appeared in rapid succession over the arm, forearm, and hand. These cutaneous tumors were readily traumatized, bled easily, and discharged a serous or serosanguineous fluid. One month prior to admission the swelling had increased to such an extent that it interfered with motion.

PHYSICAL EXAMINATION. For a complete description, the reader is referred to the detailed report on the anatomical findings in the operative specimen. Briefly, the examination of the local condition of the left upper

extremity was as follows: There was a well-healed scar of a previous left radical mastectomy without evidence of local or regional metastases. The entire forelimb was edematous, measuring at least twice the size of the opposite forearm. The skin was thick, tough, and brawny, and motion of the elbow, wrist, and fingers was limited. Scattered throughout the skin were many red or violaceous papules and macules varying in size, slightly raised, some exuding serum or blood and some crusted over. The site of the skin tumor in the upper, inner arm showed some irradiation effects, the result of ineffectual therapy. The smaller lesions in the skin of the arm measured up to 1 cm. in diameter. On the ulnar aspect there were ulcerating, fungating tumor masses, purplish in color, measuring up to 3 cm. in diameter (Fig. 3).

OPERATION. A left forequarter amputation had been performed on November 25, 1947. The immediate convalescence was uneventful; the patient left the hospital on the tenth postoperative day. Recent examination reveals possible further disease in the skin of the chest wall. Chest roentgenograms, made December 1, 1947, before the patient was discharged from the hospital, indicated the possibility of pleural metastasis. Further roentgenograms have not yet been made to confirm this finding or to determine whether it was due to a pleural reaction resulting from the operation.

Comment. This patient, who had immediate lymphedema following radical mastectomy, developed lymphangiosarcoma twenty-four years later. This was the longest interval in this series. Recurrence of cancer after such a lengthy period would be very rare. While we do not know whether the axillary nodes were involved by the original cancer, the chances are that they were not, since no postoperative roentgen-ray treatments were given.

With the discovery of these five cases, a search was begun for other patients who had developed any cutaneous lesions in the arm after radical mastectomy. One such case was discovered. As might have been expected, a biopsy of the lesion had furnished a diagnosis of Kaposi's hemorrhagic sarcoma. On review it proves to be the sixth case of lymphangiosarcoma in the lymphedematous arm.

Case 6. F.R., aged 50 years, married, came to the Breast Clinic of the Memorial Hospital in 1928. She had one child. In 1914

her left breast had been removed by radical surgery, one year after a cyst had been excised from the breast. During the interval she had been free of recurrence and had enjoyed excellent health. We have no verification of the diagnosis of cancer in this left breast.

Retraction of the right nipple ensued a year prior to her admission to our clinic, followed, five weeks later, by a fairly soft retro-areolar tumor. A diagnosis of cancer was made on the basis of the clinical examination

the right arm. Examination revealed a subcutaneous and cutaneous lesion with well-defined, slightly raised edges. Beyond the well-demarcated border there were smaller, less distinct satellite lesions appearing in a brawny, yellow, edematous skin. The entire extremity was edematous (Fig. 4).

A biopsy was reported as follows: "This section is probably to be classified as Kaposi's disease."

High voltage roentgen-ray therapy was given, the total dose being 900 r to three



FIGURE 4.

alone. At that time all patients with malignant breast tumors had preoperative high-voltage roentgen-ray irradiation. In this case a massive dose was administered to each of four ports, the treatment being completed November 14, 1928. On November 30, 1928, sixteen days later, a right radical mastectomy was performed. The report on the operative specimen was "Papillary adenocystoma—benign." This patient did not have a mammary cancer of the *second* breast.

COURSE. While the patient ran an elevation of temperature on her third, fourth, fifth, and sixth postoperative days, there was no infection or prolonged drainage. Swelling of the arm was noted on her return for follow-up and this edema persisted.

In August, 1934, six years after radical mastectomy, the patient struck her right arm on a bedpost. This called her attention to a small purplish spot on the mesial surface of

ports, repeated after two months with 700 r per port.

Following irradiation, there was moderate regression in the lesion. It became definitely lighter in color although local induration persisted. The pain diminished notably. Three months later marked pain developed in the shoulder girdle; the disease extended to the skin of the forearm and active nodules appeared in the center of the heavily irradiated skin of the arm. The arm greatly increased in size and the edema caused intense pain. Roentgenographs failed to reveal bone involvement. The patient could no longer be followed. It was reported that she had died from pulmonary metastasis.

Comment. A patient, who for fourteen years had been free of postoperative cancer of the left breast, developed a tumor of the right breast that was clinically diagnosed as

cancer. For this she had a second radical mastectomy. The lesion was a benign papillary cystadenoma. Swelling of the right arm was immediate, although her postoperative convalescence was otherwise uncomplicated.

After an interval of six years a purplish-red cutaneous and subcutaneous lesion developed on the right arm; it showed some response to roentgen-ray therapy. However, lesions appeared on the forearm, recurred in the irradiated area, and edema and severe pain increased. Death was probably due to pulmonary metastasis. Since the patient had not had evidence of mammary cancer for twenty years, the cutaneous manifestations appearing in the arm could not be considered as recurrences. The original biopsy from this lesion was diagnosed as Kaposi's disease, but with the recent review of the histologic slide it must also be considered an example of lymphangiosarcoma.

CLINICAL SUMMARY

In summary, these six cases of lymphangiosarcoma show the following: All the patients were women; half developed the initial lesion in the right breast, at an average age of more than 49 years. The youngest was 37 years of age when breast cancer appeared; angiosarcoma ensued nine years later (case 4). The oldest was 60 years, and developed the arm tumor eight years thereafter (case 3). The average interval between the breast operation and the onset of angioblastic sarcoma was twelve and one-half years; the shortest, six years; the longest, twenty-four. Two of the patients received preoperative irradiation for the breast tumor; postoperatively, one of these was found to be benign. The axillary nodes were not involved in four; the condition of the axillae is not known in the others. Only one patient had a significant postoperative elevation in temperature. None had prolonged drainage nor any postoperative complication other than *immediate lymphedema* which persisted (except that, in case 4, the lymphedema regressed for a few months after the excision of axillary scar tissue). We see, therefore, a malignant tumor arising in the lymphatics, the site of chronic

obstruction. The chronic obstruction has been the sequel of radical mastectomy.

It appears that following radical mastectomy, a moderate degree of fat necrosis occurs at the upper angle of the mastectomy scar. The entire fat layer is subsequently replaced by a fibrosis that continues down to and around the nerve, artery, and vein and is especially marked about the first portion of the axillary vein. Here a fine band of scar tissue not only compresses the vessel, but also acts as a sclerotic barrier to the deep lymphatics surrounding the vein. These lymph vessels, the brachial lymphatics that take their origin in the nodes of the cubital fossa, are well illustrated in Rouvière's anatomical description. They form the deep collecting trunks of the arm, continuing the deep trunks of the forearm, are two or three in number, and accompany not only the brachial vessels but the profunda brachii as well. They terminate in the axillary nodes where they are interrupted by axillary dissection. It is in this region, but mesial and inferior to the insertion of the pectoralis major muscle, that this constricting band of scar tissue may be observed and it is our opinion that this may be the locus of obstruction.

Be that as it may, it is obvious that a heretofore unrecognized hazard exists for the patient with breast cancer. The average five-year-cure rate for mammary cancer treated by radical surgery is about 40 per cent. Of the forty women alive and clinically free from cancer at the end of five years, 11 per cent will die of recurrent or metastatic carcinoma by the eighth postoperative year. About thirty-five survive beyond that period. Conservatively speaking some degree of swollen arm supervenes after radical mastectomy in about 70 per cent of women. This group constitutes the candidates for lymphangiosarcoma. Until this lesion is recognized as a clinical entity and ceases to be confused with recurrent mammary cancer, one cannot know its frequency and how great a hazard it may be. It is our hope that this report will influence pathologists and surgeons to recognize this tumor and that it may stimulate renewed efforts toward its prevention.

PATHOLOGY

In discussing the pathological features presented by the foregoing cases we prefer to limit the descriptions to those in which we possess the amputated extremity (cases 3, 4, and 5), for it is futile to base descriptions on small biopsy material alone, since this might be subject to several interpretations no one of which would be significant without the specific clinicopathological setting of the case as a whole. Moreover, we have made no attempt to discuss the pathology in the order of accession of cases but rather prefer to use one that will show the manner by which the final diagnostic classification was attained. Material has been selected from one case only to illustrate the microscopic findings, since that case affords the most suitable for the purpose.

We are indebted to Dr. Albert E. Casey of Birmingham for the gross description of the lesions in case 4. The specimen consisted of an edematous right upper extremity disarticulated at the shoulder joint. Distributed over the upper arm and forearm were fifteen palpable nodules measuring from 1.0 to 2.0 cm. in diameter. Nine of these were on the upper arm, six on the forearm, almost all located on the medial aspect. The various nodules all contained fresh blood under some tension, which spurted on cutting, even several hours after amputation. In addition to these a large blood-stained area of skin, that was cystic when sectioned, was situated medially in the mid-portion of the upper arm. It was said to have protruded from the surrounding skin surface previously, but had collapsed after the amputation. It contained a large amount of fluid blood, most of it apparently fresh. The hemorrhagic cysts ranged from 0.5 to 2.5 cm. in diameter. They were situated largely within the skin but extended into the hypoderm. The brachial veins showed what were thought to be thrombi. The skeletal muscle and bone showed no involvement. The anatomical diagnoses were (1) chronic lymphedema, post radical mastectomy; (2) thrombosis, deep veins of upper arm; (3) Kaposi's hemorrhagic sarcoma.

Having ourselves called attention to the

resemblance between this type of tumor and Kaposi's sarcoma, and on two occasions made an erroneous diagnosis of Kaposi's disease prior to the recognition of the present syndrome, it is easy to understand why others arrived at similar opinions. In fact, without the history and with nothing but biopsy material from a small superficial lesion, we do not see how a diagnosis of Kaposi's could be avoided. In Kaposi's sarcoma, however, we have not encountered involvement of deep veins, although Ewing quotes a paper by Philippson to the effect that this author did find such deep-vein involvement. We have been unable to verify the quotation in the original article. Rather, we believe the words forming part of the description of Philippson's case 3 were misconstrued. They read as follows: "Am Abdomen und in der rechten Thoraxhälfte, kleine, subcutane, zum Theil bläulich durchscheinende, harte, bewegliche Knötchen, die *dem Verlaufe* von Venen folgen" [*italics ours*]. That the author did not mean involvement of the deep veins themselves would appear clear from two later sentences: "Ein Zusammenhang dieser Capillaren mit grösseren Gefässen (Arterien oder Venen) ist nicht aufzufinden" and "In dem einen vollständig in Serienschnitten untersuchten Stücke liess sich aber sonst an dem ganzen Gefässsystem, sowohl an den Arterien, als an den Venen, keine weitere Veränderung entdecken." Following the course of veins does not necessarily imply location within them.

Certainly, there is no reason why true Kaposi's disease could not occur in the swollen arm of the postmastectomy patient, but that it should do so without manifestations in other skin areas would be most unlikely; and one must place the present process in another category. In some instances of Kaposi's disease there is a history of prior edema in the part where the first lesions initiate, for example, the edema with varicose ulcers, but the association is obviously incidental and foci of additional new primary disease occur in other regions where there is no edema. Late edema in fully developed Kaposi's sarcoma naturally is common but this edema follows the disease rather than initiates it. Hence, despite superficial resem-

blances, any question of the identity of the present syndrome with Kaposi's hemorrhagic sarcoma is answered in the negative.

Whereas no doubts remain in our minds as to the identity of the tumors in these six patients, it is unfortunate that in but one instance do we possess the amputated extremity accompanied by a gross description that we can regard as fully adequate and in which the lesions are traceable beyond doubt to their foci of origin. This is case 5. The tentative diagnosis was already known so that an effort was made to develop as far as possible our thesis of the nature of the lesion. A description follows:

The specimen in case 5 consists of an interseapulothoracic (forequarter) amputation of a left upper extremity. Its overall length is 67 cm. The skin presents a striking appearance, revealing three types of lesions. The first is a general thickening both of skin and subcutaneous tissue together with a moderate pitting edema, involving the lower two-thirds of the upper arm where the skin thickness averages from 0.4 to 0.6 cm. Over the forearm there is a similar thickening together with wrinkling that produces a mosaic pattern with units 0.5 to 0.7 cm. thick. The dorsum of the wrist is pachydermatous; the skin shows a great deal of longitudinal and transverse wrinkling, giving it a "tree bark" appearance; the skin thickening ranges from 0.7 to 0.9 cm. There is transverse wrinkling over the dorsum of the hand extending on over the proximal phalanges. Puffy edema is present. The skin thickness over the phalanges measures 0.2 to 0.3 cm.

The second lesion comprises six discrete, red to purple polypoid tumors. The first, situated on the medial aspect of the middle third of the upper arm, measures 4 cm. in diameter. It projects a maximum distance of 1.5 cm. above the surface of the surrounding skin but extends only slightly below the skin surface. It is flattened on top, has a wide base, is soft, shows various shades of red to purple color, and, on section, reveals a darker, soft, reddish periphery with a grayish-red, softer central core. The second tumor, 1.5 cm. in diameter, is located on the medial aspect of the anterior surface of the

forearm 7.5 cm. below the elbow. It is elevated 0.8 cm. above the surrounding skin, and is largely necrotic. A third tumor is 2.5 cm. in diameter, extends 1.0 cm. above the skin surface and 0.5 cm. into the subcutaneous tissue, and is centrally ulcerated. A fourth occupies the lateral aspect of the forearm a few centimeters below the elbow. This lesion is similar to the others except that it has a central cystic cavity. A fifth tumor occurs further distal on the forearm, and a sixth on the dorsum of the hand just proximal to the base of the phalanx of the fourth finger. Whereas these six lesions are designated as the tumors, reference to the color illustration will show transitions between these and the earlier phases discussed next.

The third type of lesion is the most striking. It consists essentially of myriads of pinkish-red to purplish-red papules that average 0.4 to 0.8 cm. in diameter and rise no more than 0.1 to 0.2 cm. above the skin surface. For the most part they are discrete but, in some areas, confluent with a diameter of from 2.0 to 5.0 cm. They appear to cover half the surface of the lower part of the upper arm and are most prominent on the anterior and lateral aspects. They also occupy about one-fourth of the skin surface area of the forearm, again largely as discrete papules but with some zones of confluence. Distally they extend over the dorsum of the hand to within a short distance of the base of the phalanges. Only one lesion is present on a finger—an ulcerated tumor, 2.0 cm. in longest dimension, on the medial aspect of the dorsum of the fourth finger. The papular lesions are usually light red in color, but a few are bluish or black and occasionally appear as brownish macules. Occasional linear telangiectases are seen. Attention should be called particularly to the ulcerated lesion of the phalangeal skin, since this was later shown to be entirely different from the rest of the disease.

Next let us consider the deeper lesions. The dissection of the arm shows the scapula and attached muscles grossly normal except for a small hemorrhagic area in the collum scapulae. There is one small pinkish-red nodule, 0.8 cm. in diameter, lying in the infraglenoid

fossa. The subcutaneous tissues of the lower half of the upper arm, the forearm, and the wrist show many bright red, soft, friable areas varying in size from a few millimeters up to some 3.0 cm. in diameter. Many of these foci suggest tumors in the veins; and what are definitely small vessels plugged with soft, red, friable material are found in the tissues of the antecubital fossa and the dorsum of the arm. One major tributary of the brachial vein is plugged by red, friable material 8 cm. proximal to the elbow. Small subcutaneous veins are similarly blocked. No gross lesion appears in the other major veins nor in the entire arterial tree.

All the subcutaneous tissues are greatly thickened and show what is apparently an increase of fibrous tissue together with many thin-walled vessels. The tissue contains much thin, yellowish fluid in which fat globules can be seen. Only two areas of the muscles show change. A diffuse, infiltrating, soft, red, friable mass, 5.0 cm. in diameter, that involves the triceps brachialis septum and both muscles, especially the brachialis, is found in the mid-portion of the upper arm. A similar

mass involves the extensor group of muscles of the forearm a few centimeters proximal to the wrist as well as the subcutaneous tissue of the dorsum of the hand.

The humerus is 29 cm. long and of normal configuration, as are the other bones of forearm and hand. Sagittal section of the humerus disclosed a marrow cavity filled with soft, gelatinous, reddish-purple material that begins 2.5 cm. below the most proximal portion of the head and extends downward to a line 10 cm. above the epicondyles. A similar process occupies the upper 8 cm. of radius and small, red foci occur in the mid-portion of the ulna. The carpal and metacarpal bones, and phalanges are not remarkable. Their marrow is yellow.

At this point it should be said that prior to dissection an effort was made to secure vasograms by injecting radio-opaque material (sodium iodide). At that time some doubt remained in our minds as to whether the tumors were derived from blood vessels or lymphatics, a question later answered without any need for accessory evidence. The radiographs proved of no assistance.



FIG. 5. Follicular lymphoid deposit; the proliferating lymphatics at top suggest an attempt to form a peripheral lymph sinus.



FIG. 6. *Proliferating lymphatics of subcutaneous tissue; the neoplastic quality is questionable.*

The larger local cutaneous tumor masses were opaque, it is true, but it was questionable whether this opacity exceeded that which might occur in soft-tissue roentgenograms without injection. Deeper vessels were not visualized.

When sections of these larger tumors became available, there was much necrosis, and the tumors were solid and relatively avascular. Suffice it to say that circulatory continuity between tumor vessels and general circulation could not be shown.

Eighty blocks of tissue were prepared for study. These were fixed in formalin and Zenker's solution. Sections were stained in routine hematoxylin and eosin, phosphotungstic acid hematoxylin, and for reticulin and elastic tissue.

The epithelium shows areas of hyperkeratosis, comparable to those seen at times in

lesions which the dermatologists latinize in the term "lymphangioma circumscriptum cutis cysticum." Foci of bullous edema are adjacent to the ulcerating projecting tumors. A pronounced fibrinous edema, both diffuse and slightly concentrated, occurs in the subcutaneous tissue about sweat glands and small venules. Connective-tissue bundles appear wide and one gains the impression that there is a true increase in the amount of coarse collagenous tissue. Much of this increase is perhaps apparent only because the individual fibers making up the bundles are separated by edema. Fibroblasts are not numerous. Between the coarser bundles, the connective tissues remind one of a dense spider-web network of extremely fine fibrils. There is a mild degree of fat necrosis with foci of fibrinous edema. A cellular infiltration that is often diffuse extends throughout the entire thick-

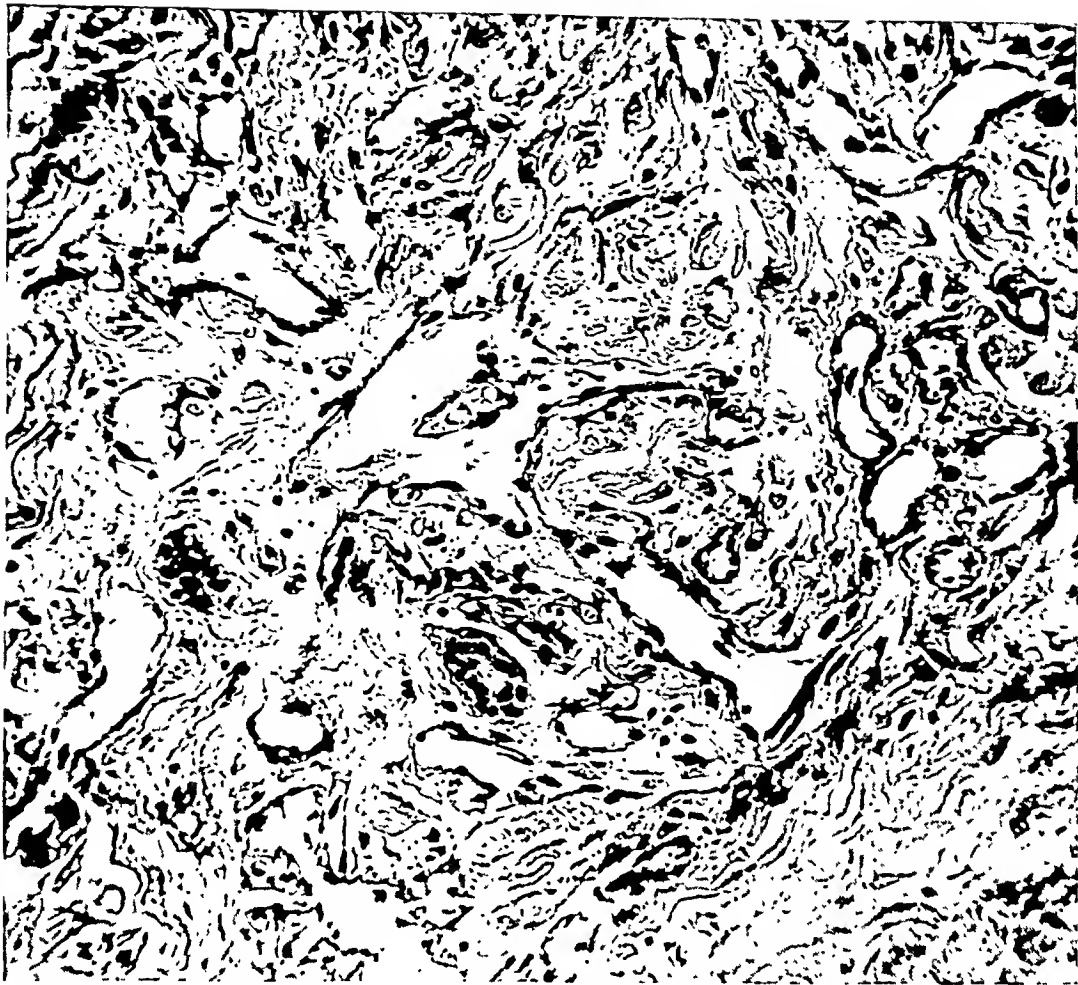


FIG. 7. *Lymphangiomatosis in subcutaneous tissue.*

ness of the connective tissue. Much old and fresh hemorrhage has occurred, not only in the actual tumors but also in the loose edematous connective tissue, and especially in the zone where the ulcerating tumor is found.

Most of the cells are lymphocytes although plasma cells are numerous. Monocytic elements are sparse. The mononuclear phagocytes are heavily pigmented. Not only are lymphocytes scattered diffusely but there are numerous closely packed aggregates, some with clearer germinal centers, recalling the follicular aggregates often seen in hygroma cysticum. The distribution of the surrounding lymphatics suggests an attempt to form a peripheral sinus. No significant amount of edema occurs in such structures as dermal muscle or cutaneous perineural tissues. Small veins may be thrombosed. Occasional organized thrombi with recanalization can be seen in small arterioles and fibrin thrombi in tiny lymphatics.

Numerous dilated proliferated lymphatics occur in the subcutaneous tissue and, deeper, in the intermuscular fascia. Where a definite locational pattern can be discerned, these dilated lymphatics appear to occur particularly about the veins. Frankly, it has not been possible for us to say when the process surpasses a stage of lymphatic dilatation and multiplication and must be designated as neoplastic. The change is gradual with absolutely no sharp line of distinction. When the endothelial cells lining the lymphatics reach a certain size, when they appear enlarged so that their nuclei bulge into the lumina, when the nuclei attain some degree of size and hyperchromatism, we have accepted the process as neoplastic. Again there is every transition from the stage in which tumor cells still line channels up to that of diffuse or circumscribed solid growth. One sees lesions of multiple origin in every phase of development.

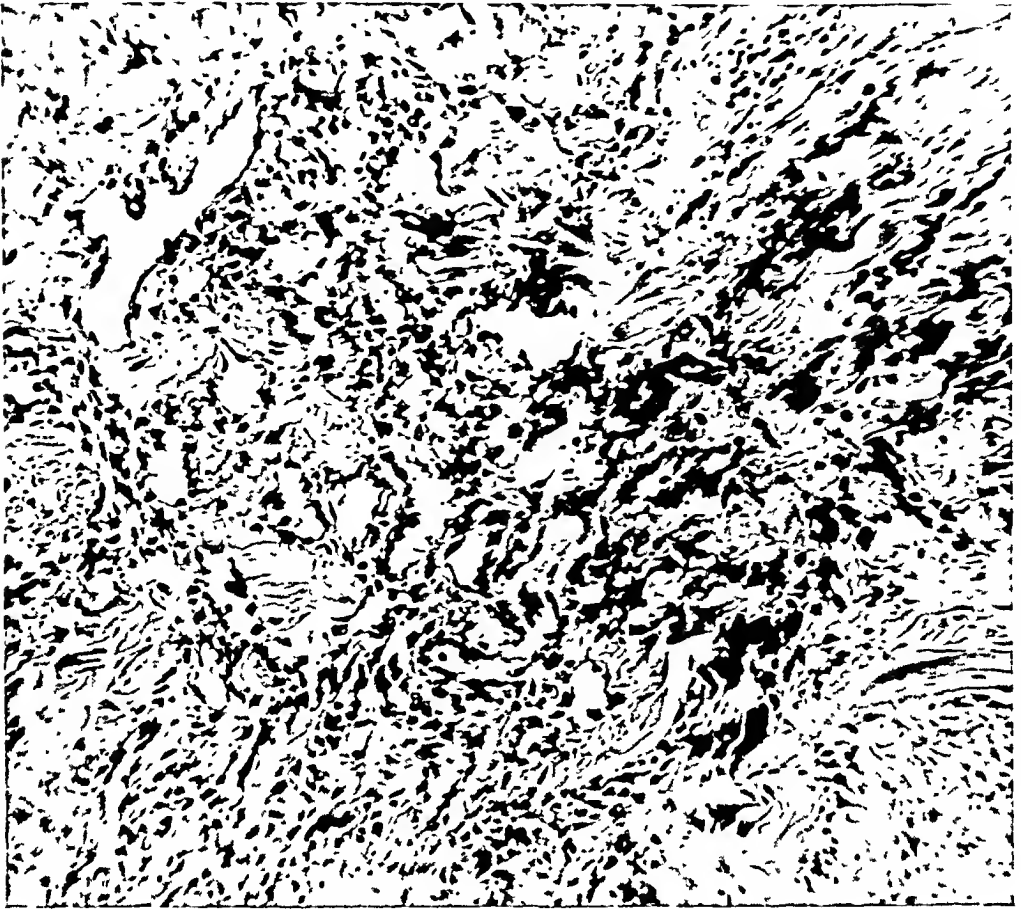


FIG. 8. *Early lymphangiosarcoma.*

In the early stages, the lymphatic channels are free of blood cells or contain relatively few red cells. Lymphocytes within the channels are common; monocytic cells, rather rare. Vessels in the vicinity of the larger solid tumors, however, may contain much blood, especially where necrosis and interstitial hemorrhage has taken place. It is in such areas that, without support derived from early stages of the process, one might be justified in a diagnosis of hemangioendothelioma, especially since these blood-filled sprouts seem to overgrow into zones of necrosis like granulating vessels. Moreover, smaller vein walls are often thickened, which remind one of the appearance seen in arteriovenous aneurysms.

The mode of involvement of the larger veins is of interest. These do not appear to be involved by extension of the solid tumors into the vein lumina from adjacent local tu-

mor, but rather the solid tumor within the vein appears to arise directly from the lymphatics surrounding the vein and actually within the vein wall. That subsequent embolic spread of solid tumor may occur is evidenced from case 4, in which the autopsy showed the lungs filled with many areas resembling hemorrhagic infarction and amid these areas, numerous foci of tumor resembling that found in the arm. Comparison of lung lesions with the previously removed primary breast cancer shows no similarity. This patient (case 5) is already exhibiting spread of the disease to the trunk.

As to the hemorrhagic areas in the bones: this is not tumor, but only interstitial hemorrhage. So, too, is the area described in the infraglenoid fossa. No disease appears in any lymph node. Reference to the gross description, however, will recall the existence of one ulcerated tumor occupying the dorsomedial

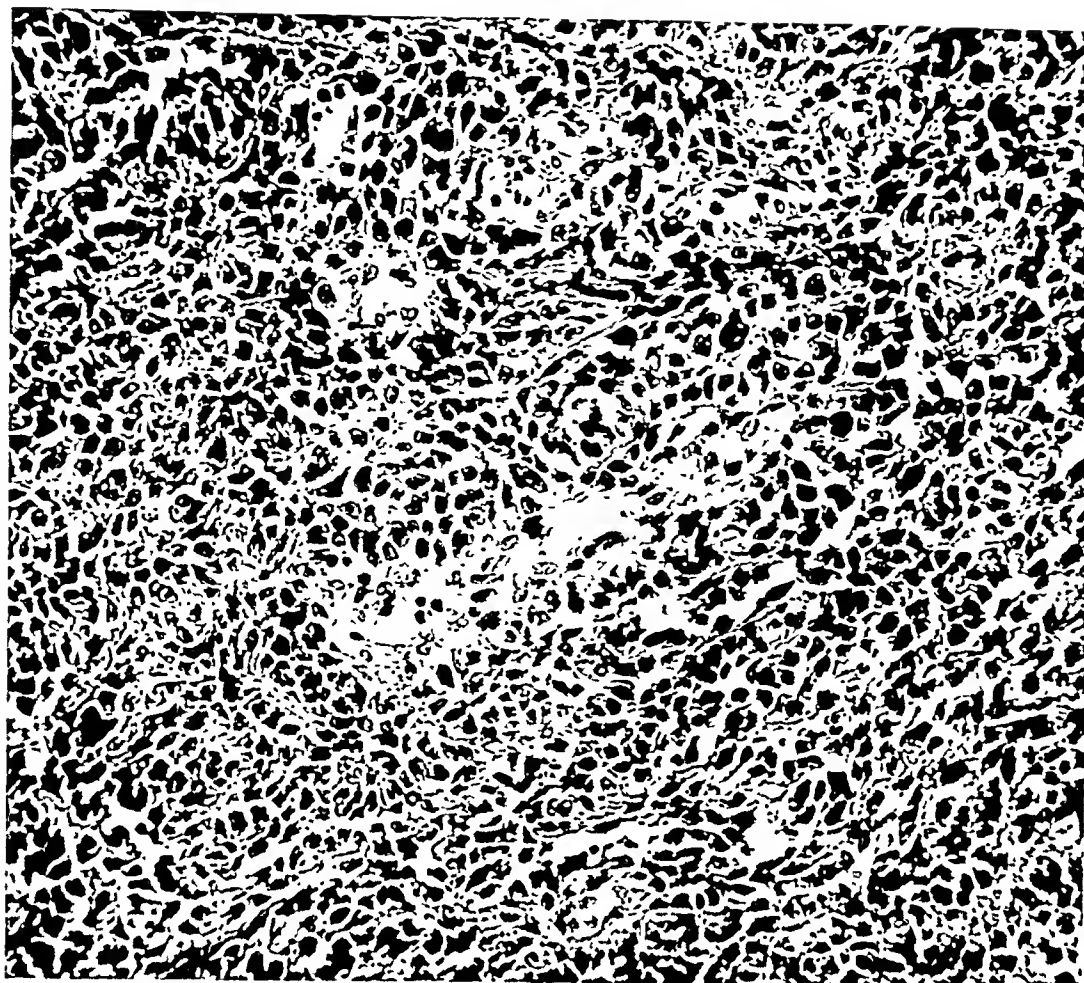


FIG. 9. *Solid anaplastic lymphangiosarcoma; ulcerating cutaneous tumor.*

aspect of a phalanx. Grossly, this lesion is different from the others and it proves to be still another primary cancer, a typical squamous carcinoma.

The specimen from case 3 consists in a forequarter removed by interscapulothoracic amputation. Longitudinal measurements are recorded but possess no significance. Circumferential measurements are: mid upper arm, 26 cm.; mid forearm, 18.5 cm.; wrist, 16.5 cm. A considerable contracture existed at the elbow. From the distal fold at the wrist to the proximal limit of the middle third of the upper arm the skin is firm, indurated, and covered by multiple bluish nodules, some projecting slightly, others depressed. There are some thirty-five on the ventral aspect and twenty-five on the dorsal. None is ulcerated. Depressed areas, the largest of which is 5×5 cm., are firm to palpation. Projecting areas appear cystic and on section yield from 1 to

4 cc. of dark hemorrhagic fluid. The largest of these measures $1.5 \times 1.0 \times 0.5$ cm. No lesions occur on the hand, upper half of the arm, or attached shoulder area.

On incision the tissues are wet and ooze clear fluid. The subcutaneous tissue is pale yellow and contains many soft, nodular, hemorrhagic foci. It appears adherent to the underlying fascia and in places to tendon and muscle, particularly about the elbow joint. The superficial veins contain fresh clots. The subcutaneous tissue measures 2.25 cm. in thickness at the upper aspect of the arm; 1.25 cm. in the mid-upper arm; 1.5 cm. in the antecubital fossa; 1.25 cm. on the forearm; 0.5 cm. at the wrist. The hemorrhagic tumor involves triceps, biceps, and brachialis muscles about the elbow joint and invades the tendons of the biceps and the flexor carpi radialis. The major vessels, both arteries and veins, show no gross evidence of disease.

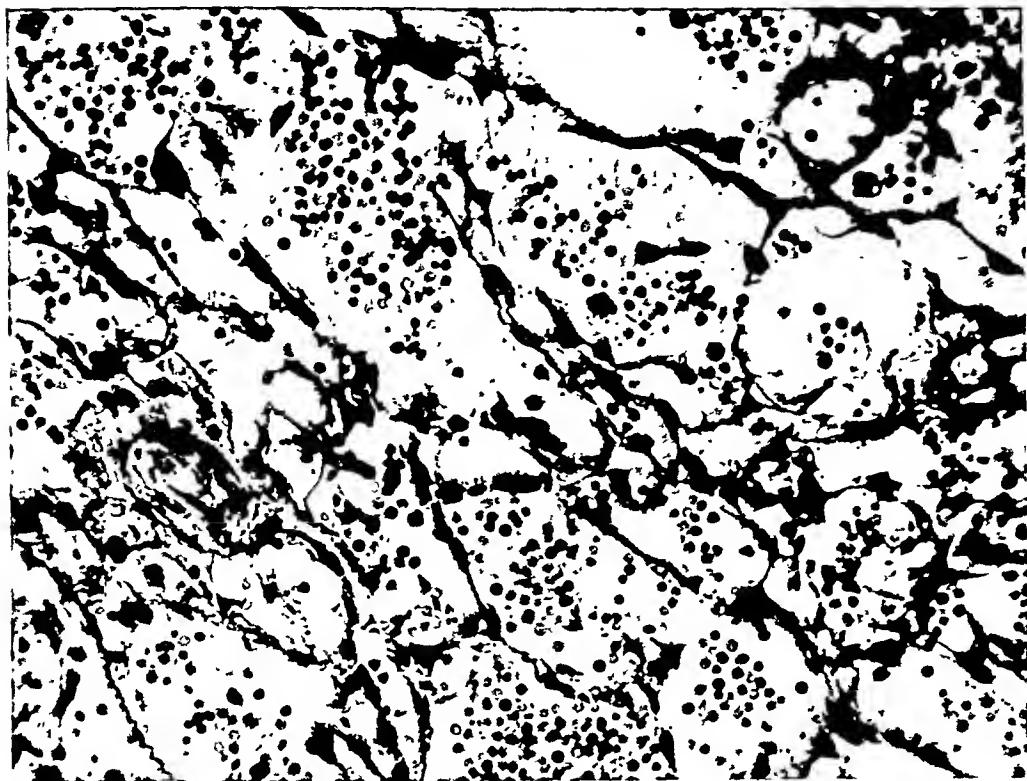


FIG. 10. *Lymphangiosarcoma with much hemorrhage; the growth pattern is suggestive of granulation tissue.*

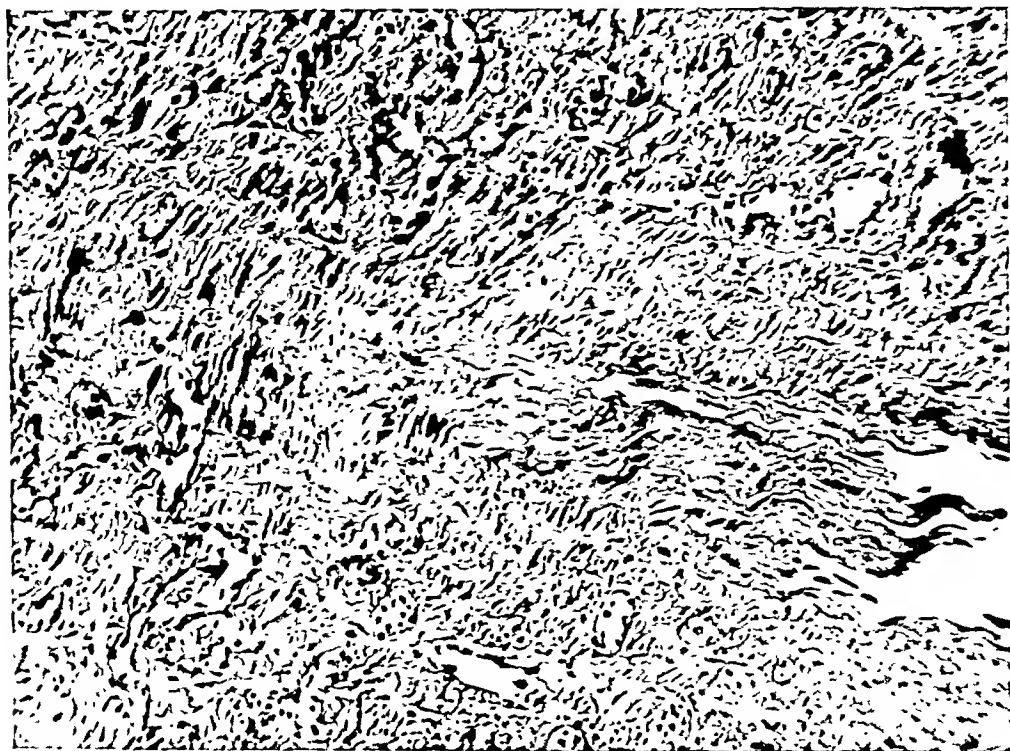


FIG. 11. *Lymphangiosarcoma in the perivascular lymphatics about a deep vein.*



FIG. 12. *Lymphangiosarcoma invading the wall of a deep vein; elastica stain.*

No abnormal features were observed when the various bones were sawed through. No lymph nodes are involved.

In case 3 twenty-nine blocks are available for study. The stains used included routine hematoxylin and eosin, trichrome, elastica, and reticulin. In this case it is unfortunate that materials selected for study were more designed to investigate the structure of the obviously malignant lesions than to afford opportunity to trace these to tissues of origin. Hence stages in the development of the process are somewhat less clearly apparent. The same keratoses occur in some areas of the skin, but in others the skin appears thin and atrophic. Keratotic plugs occur in hair follicles. Edema of the connective tissues, both subcutaneous and deep, is prominent although less so than in case 5. The same fat necroses are seen. Edema is quite prominent in certain vein walls and in both the perineurium and the endoneurium of deep nerves. Medium-sized veins are thickened, rarely thrombosed, and the muscle tissues of their walls are separated by fibrinous edema. Foci

of necrosis and regeneration in the deeper striated muscle adjacent to the tumor in the related fascia and tendon comprise a feature not seen in other cases.

The same diffuse and localized follicular lymphoid infiltration is present. Multiplication of small lymphatics, both superficial and deep, is seen, but, perhaps from lack of sufficient material for microscopy, clear-cut transitions from lymphatic endothelium into solid tumor is much less easy to ascertain than in case 5. In fact it is seen but rarely. The tumors when fully developed are very hemorrhagic. There is much diffuse interstitial hemorrhage and much pigmentation. Still in what are the earliest stages of neoplasia, the points of origin are dilated vessels situated *about* smaller venous channels or in the subcutaneous tissue, not clearly related to venules. These are surely lymphatics. We do not find tumor *within* the veins. What in the gross might suggest such proves only hemorrhagic tumor adjacent to or surrounding the vein. No organized elastica exists to map out a vein wall about any of the solid nodules.

In none of our cases has tumor been traced to cells of "tissue spaces" and the only suggestion of such origin has been in small biopsy material where the trauma of the procedure might conceivably falsify the picture. Where origins can be traced, one always finds them in formed channels—channels with definite endothelial walls.

In case 4, far fewer sections are available for study and their interpretation is consequently more difficult. Certainly the solid tumors resemble those of cases 3 and 5. They are more hemorrhagic. The smaller beginning lesions, those that we interpret as dilated lymph channels, contain more blood and, without the aid of the preceding cases described in detail, one would be at a loss to decide whether they were capillaries or lymphatics. Neither is the mechanism of vein involvement clear. In favor of lymphatic origin, however, is the thick lymphocytic cuffing; and the numerous follicular lymphoid deposits again bespeak this origin. Stains for elastica were not available, nor were they of assistance in the previously described cases, for in the early lesions one could only say that an elastica was absent.

CONCLUSION

The basis for the development of tumors of the type described in lymphedematous arms

following radical mastectomy is naturally obscure. One would like to speculate upon the existence of a systemic carcinogenic factor responsible not only for the lymphangioblastic tumors but likewise for the initial mammary cancers, and in the one case for the squamous carcinoma of the skin. It would surely be remarkable were the lymphedema alone the predisposing factor, for in other diseases involving chronic lymphedema, e.g., filariasis, one does not find these tumors reported. In our experience they are peculiar to the obstruction following radical mastectomy. They have occurred without axillary metastases of the breast cancer, with or without postoperative irradiation, and arise in sites where no irradiation has been administered. Hence the hypothesis of a systematic carcinogen is attractive, something acting in a locus minoris resistentiae. Unfortunately, however, in the case of one patient we have no confirmation pathologically of the existence of the breast cancer. If we accept the clinical diagnosis in this case, the correlation (breast cancer, lymphedema, lymphangioblastic sarcoma and in one instance likewise squamous cancer, together with the absence of similar tumors in unrelated types of lymphedema) renders it impossible to discard the thesis proposed—that of the existence of a systematic carcinogen.

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EVOLUTION OF CANCER OF THE UTERINE FUNDUS IN THE RABBIT*

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COMPARATIVELY little investigative work has been directed toward a clarification of the sequential relationships in the origin of cancer. The older conception, that cancer arose as a sudden transformation of normal cells, is not supported by experimental evidence. On the contrary, there is evidence to suggest that it is the final stage in a developmental process and that its identifying biological attributes are not present initially, but rather, are attained by gradual evolution.²

Exploration of the problem has been hindered by the lack of suitable material. Comparative morphological and biological studies of tumors at various intervals after inception are required and this necessitates repeated biopsy. Human patients will not tolerate such a procedure, while the size of mouse tumors together with the operative difficulties involved generally precludes their use. During the past few years, however, a considerable series of tumors have been found in the rabbit and their ready accessibility allows pertinent experimentation.

MATERIALS AND METHODS

The experiments to be reported comprise a continued investigation of adenocarcinomas of the uterine fundus in the rabbit. These tumors have been studied in some detail^{1,3,4} and possess characteristics that render them particularly suitable for studies of the present type. The antecedent history of tumor-bearing animals is almost pathognomonic, and the actual presence of the growths can be detected by palpation through the abdominal

wall when they have reached a diameter of 0.5 cm. The tumors grow to a large size during early stages so that abundant tissue is available for study throughout their development. Their course is relatively slow, extending over a period of one to two years, but development to cancer is certain and the eventual termination is metastasis.

The primary object of the experiments was to study and to compare the transplantability and growth rate of the cancers at different phases of development. To this end, laparotomies were performed at various intervals after the discovery of the tumor and representative fragments removed for investigation. Portions of the fragments were fixed for histological study and homologous and autologous transplants made with the remaining tissue.

It should be emphasized that the term "homologous transfer" is used here to refer to the transfer of cancer tissue to normal, unrelated animals of the same species and has a different significance than when used, as in mouse-tumor research, to mean transfer to an animal of the same strain. In the present context, it signifies transfer to a normal and comparatively constant environment possessing as distant a relationship to that of the primary host as is possible within the species. The behavior of the homologous transplant, therefore, reflects the constitution of the tumor at the time of transfer, for it has been removed from the influence of those factors concerned in its genesis and prior development that operate in the primary host and that may well form an integral part of the genetic make-up of animals of the same inbred strain. For these reasons, routine homologous transfer was employed to determine the progress of developmental changes in the tumor itself, independent of factors resident in the primary host.

Autologous transfer was carried out in

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* This investigation was aided by grants from the Jane Coffin Childs Memorial Fund for Medical Research, The Donner Foundation, and the David, Josephine and Winfield Baird Foundation.

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Received for publication, November 19, 1947.

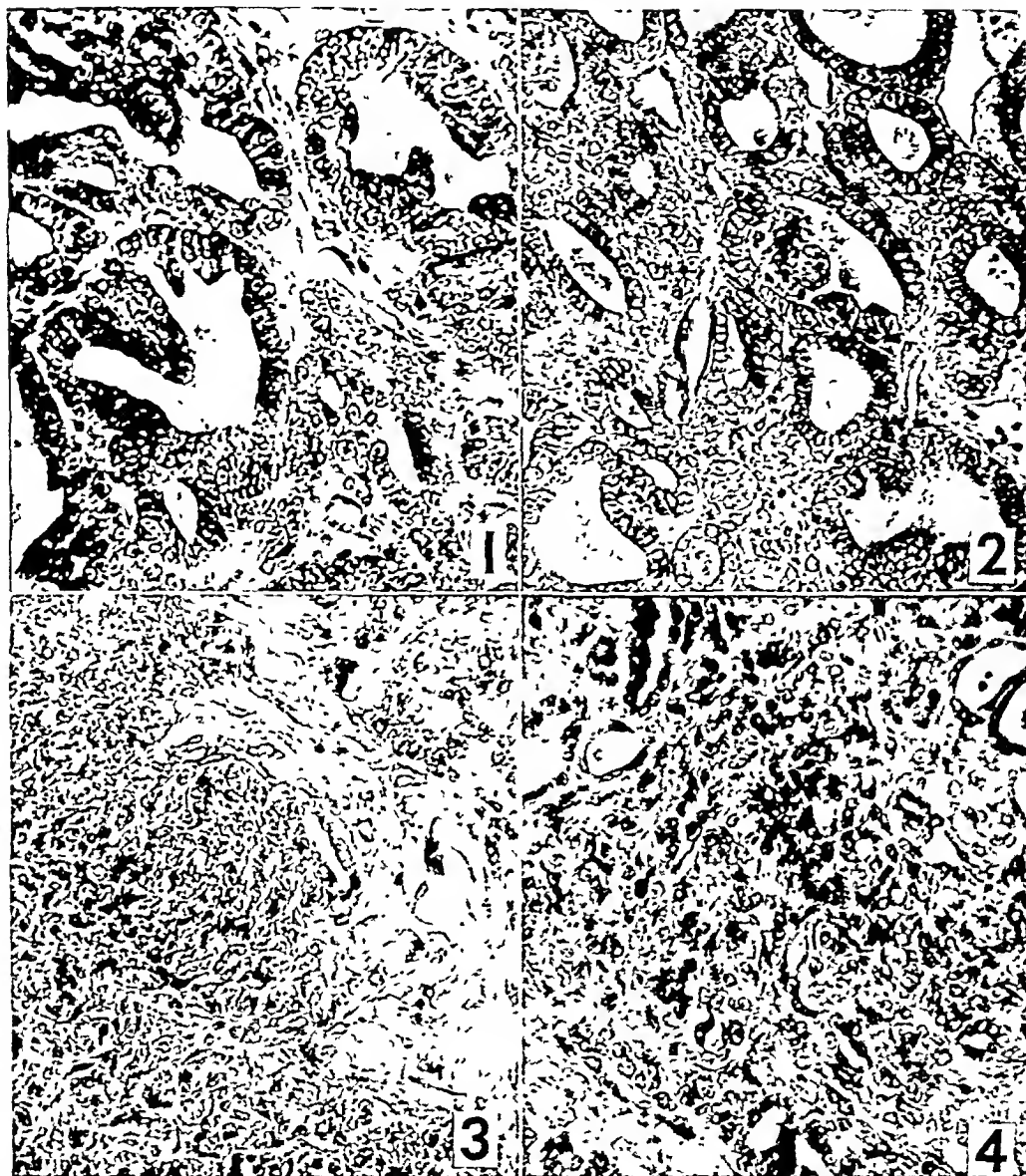


FIG. 1. Case 1 (BE31-3). Section of uterine tumor obtained at laparotomy on November 9, 1939, showing a Grade-2 growth.

FIG. 2. Case 1 (BE31-3). Section of uterine tumor obtained at laparotomy on November 11, 1940. Comparison with Fig. 1 shows no appreciable change in organization in the year's interim.

FIG. 3. Case 1 (BE31-3). Section of autologous subcutaneous transplant of tumor tissue made on November 9, 1939. The section was obtained at autopsy seventeen months after transfer and shows a loss of organization as compared with parent tissue (Fig. 1).

FIG. 4. Case 1 (BE31-3). Section of uterine tumor obtained at autopsy showing a comparable loss of organization (Grade 3).

All sections were stained with hematoxylin and eosin; all $\times 350$ photographs.

TABLE 1

LAPAROTOMIES AND TRANSPLANTATION PROCEDURES PER

Case No.	Animal No.	Date of Birth	First Laparotomy		Second Laparotomy			Third Laparotomy		
			Date	Transfer	Date	Transfer		Date	Transfer	
				Auto. Homo.		Auto. Homo.			Auto. Homo.	
1	BE31-3	12/17/33	9/11/39	S-c†	o	11/11/40	o	o		
2	D183-4	5/ 7/34	5/ 6/37	S-c	o					
3	D183-5	5/ 7/34	2/ 9/40	S-c	Eye					
4	HA550-2	5/19/37	2/21/40	o	o	5/24/40	o	o	8/16/40	o
5	HA586-4	12/ 3/37	2/27/40	o	o	10/ 2/40	o	o	1/16/41	o
6	MA13-1	3/13/36	3/ 4/40	S-c	Eye					o
7	MMA10-2	2/ 9/36	11/18/39	S-c	Eye	2/29/40	S-c	o	12/ 5/40	o
8	X383-3	11/ 7/32	10/26/37	Eye	Eye	3/22/38	o	o	10/31/38	o
9	X1605	12/27/33	3/22/38	o	o	6/ 7/39	S-c	Eye	11/17/39	o
10	X1800-2	2/13/34	6/ 1/39	Eye	Eye	11/18/39	Eye	Eye	1/24/40	Eye
11	X2332-7	5/13/34	11/16/39	S-c	Eye	2/28/40	o	o		
12	X2673-6	1/18/34	10/24/39	Eye	Eye	2/14/40	o	o	4/ 6/40	o
13	X2678-7	7/ 8/34	5/31/39	Eye	Eye	11/21/39	S-c	Eye		
14	X4089-2	1/ 7/35	2/14/40	S-c	Eye					
15	X5728-5	4/ 8/35	6/ 1/39	S-c	Eye	11/20/39	S-c	Eye	2/28/40	S-c
16	X6101	5/ 6/35	10/15/40	S-c	o	7/ 1/42	o	Eye		o
17	X6365-2	5/29/35	10/31/39	S-c	Eye	2/21/40	S-c	o	4/10/40	o
18	X7634-3	3/13/36	11/14/39	Eye	Eye	2/23/40	S-c	o	4/12/40	o

many cases to determine the behavior and fate of the tumor at different sites in the primary host. In evaluating the results of such transfers, it should be borne in mind that the autologous transplant, unlike the homologous, is subject to the continued action of host factors so that changes are to be expected in its morphology and biological behavior comparable to those in the primary uterine tumor.

In the majority of cases, laparotomy was not performed until the uterine tumor had attained a diameter of 1 cm. Tumor tissue obtained at earlier developmental stages grows readily when transplanted elsewhere in the primary host but invariably fails to survive homologous transfer; hence, since the present investigation involved a study of growth rates in normal animals, very early tumors were not used.

Subsequent laparotomies and transfers were carried out at varying periods throughout the remainder of the life of the host, and a complete autopsy was performed at death. The various laparotomies and transplantation procedures are outlined in Table 1.

DEVELOPMENT OF THE PRIMARY TUMOR

Morphological Development. The morphological development of the tumors has been followed in a large number of animals by biopsies repeated at monthly intervals. In the usual uncomplicated cases, architectural changes occur in a definite sequence suggesting a gradual loss of organization from inception to metastasis. Such changes in organization have been utilized in developing a system of grading for use in comparative studies. Other systems based on invasion, degree of differentiation, or mitotic index have proved less satisfactory. Biopsy specimens rarely contain uterine muscle and the presence or absence of invasion cannot always be determined unequivocally; changes in cellular differentiation observable in hematoxylin-eosin preparations are not of sufficient degree to permit classification; and, finally, mitotic indices have not been in agreement with the growth rate determined by actual transfer.

Very early tumors consist of a simple reduplication of well-formed endometrial glands separated by abundant stroma. Such

TABLE 1.

FORMED DURING THE COURSE OF TUMOR DEVELOPMENT

Case No.	Fourth Laparotomy				Fifth Laparotomy				Sixth Laparotomy				Autopsy		
	Date	Transfer			Date	Transfer			Date	Transfer			Date	Transfer	
		Auto.	Homo.			Auto.	Homo.			Auto.	Homo.			Homo.	Hetero.
1													4/14/41	Eye	
2													3/ 9/38		
3													11/22/41	Eye Test.	Eye
4	12/22/41	S-c	Eye										4/ 2/42	Eye	
5	8/14/41	o	o		7/5/42	o	Eye		2/ 2/43	o	o		3/23/43	Eye	
6													12/20/41		
7													9/ 2/41	Eye Test.	Eye
8													2/23/39	Eye	
9													11/22/39		
10													1/ 6/41	Eve Test.	Eye
11													11/15/40	Eve Test.	
12													9/16/40	Eve	Eve
13													12/22/39	Eve	Eve
14													2/ 9/42	Eve	
15	4/ 5/40	o	Eve										7/24/41	Eve	
16													7/ 6/42	Eve	
17	9/20/40	o	Eve										11/ 1/40	Eve	
18													9/30/41	Eve	

‡ S-c = subcutaneous space. eye = anterior chamber of eye, test. = testicle.

an organization is referred to as Grade 1; tumors of this stage were not used in the present study. Subsequent alteration proceeds in either of two ways. Rarely, the reduplication of small acini continues, gradually replacing the stroma, until the microscopic picture comes to resemble that of a fetal adenoma of the thyroid. The second mode of progress is much more common and consists essentially in the assumption of a papillary architecture. Acini enlarge, some become cystic, and papillary projections grow into their lumina. The papillomas are uniradicular at first but rapidly become multiradicular. Their branches unite with each other and with the branches of adjacent growths to form pseudoacini in an extremely complicated arrangement somewhat comparable to that found in duct papillomas in human breasts. Such organizational types are referred to as Grade 2 and are characteristic of the 1 cm. tumors found at the first laparotomy in the present series of cases (Fig. 1). In Grade-3 tumors, the acinar and papillary patterns of the two types become less distinct. Areas of diffuse cellular growth

without discernible architecture appear, but the general glandular organization of the tumors remains apparent (Fig. 4). Grade 4 is reserved for the final developmental stage in which cellular growth is diffuse, disorganized, and lacking any indication of glandular pattern (Fig. 5).

The grades assigned to the various biopsy and autopsy tissues are recorded in Table 2. The point to be stressed, primarily with reference to this table, is that the morphology of the tumor did not remain static in the majority of cases. In thirteen of the eighteen animals, the tumor progressed from a Grade-2 growth at the first positive biopsy to one of Grade 3 or 4 at autopsy. The change in grade occurred relatively late in the course of development and was shortly followed by death. The change was not a sudden transformation, however. Gradual transitional changes, noted in consecutive biopsy specimens, are not apparent under the present grading system and their exposition would require an amplification of data too bulky for tabular presentation.

TABLE 2.

THE DEVELOPMENT OF THE UTERINE TUMOR WITH REFERENCE TO GRADE OF ORGANIZATION AS DETERMINED FROM TISSUE OBTAINED AT VARIOUS LAPAROTOMY EXAMINATIONS AND AT AUTOPSY

Case No.	Animal No.	Grade at Laparotomy						Grade at Autopsy	Remarks	
		First	Second	Third	Fourth	Fifth	Sixth	Prim. Metas.		
1	BE31-3	2	2 (12) *						3 (17) 4	Coincident carcinoma of vaginal wall with metastasis.
2	D183-4	2							3 (10) 3	
3	D183-5	2							3 (21) 4	
4	HA550-2	CH†	2 (3)	2 (6)	3 (22)			3 (26)		
5	HA586-4	CH	CH (7)	CH (11)	2 (18)	2 (29)	2 (35)	2 (36)	Carcinosarcoma.	
6	MA13-1	2								2 (21)
7	MMA10-2	2	2 (3)	2 (13)						3 (22) 4
8	X383-3	2	2 (5)	2 (12)						2 (16) 2
9	X1605	2	2 (15)	2 (20)					2 (20)	Coincident sarcoma of uterus without metastasis.
10	X1800-2	2	2 (6)	2 (8)					4 (20) 4	Coincident carcinoma of breast without metastasis.
11	X2332-7	2	2 (3)					4 (12) 4		
12	X2673-6	2	2 (4)	2 (6)					3 (11) 3	
13	X2678-7	2	3 (6)					4 (7) 4		
14	X4089-2	2							3 (24)	
15	X5728-5	2	2 (5)	2 (8)	2 (10)			3 (25) 4		
16	X6101	2	2 (21)					2 (21) 4		
17	X6365-2	2	2 (4)	2 (6)	3 (11)			3 (12) 4	Coincident carcinoma of vaginal wall with metastasis.	
18	X7634-3	2	2 (3)	2 (5)						3 (23)

* Figures in parenthesis refer to the interval in months since the first laparotomy.

† CH = cystic hyperplasia.

Five of the tumors remained comparatively static throughout their course (cases 5, 6, 8, 9, and 16). Metastasis occurred in only two of these cases. In case 8, the metastatic growths were identical in appearance with the tumor found at laparotomy sixteen months previously. In case 16, all of the secondary foci showed a complete loss of architectural arrangement despite the fact that the primary tumor remained well organized (Figs. 13 to 17). This case is of special interest and will be considered further in a later paragraph. It is pertinent to note here, however, that the animal bore a second spontaneous tumor, a carcinoma of the breast; this constitutes the only instance in this series of metastasis of the uterine neoplasm in the presence of a co-existing tumor.

Six of the animals were free of metastases at death. As just stated, the primary tumors in three of these showed no morphological progress during life. Two others (cases 4 and

18) bore co-existent carcinomas of the vaginal wall. Thus with one exception (case 14) the absence of metastasis was associated with either a static primary growth or a coincident tumor.

In half the cases, the metastatic growths and the primary tumor were of the same grade at autopsy; in the others the metastases showed a less organized structure. Curiously, the course of the disease was significantly shorter in the former group, averaging twelve months, in contrast to nineteen months in the latter.

Case 7 is of particular interest morphologically. Biopsy specimens obtained at the first three laparotomies all showed straightforward adenocarcinoma while autopsy sections of the uterus contained both adenocarcinoma and sarcoma with the sarcoma actually invading the carcinoma. Some of the metastases were purely sarcomatous, others contained only adenocarcinoma, and still others

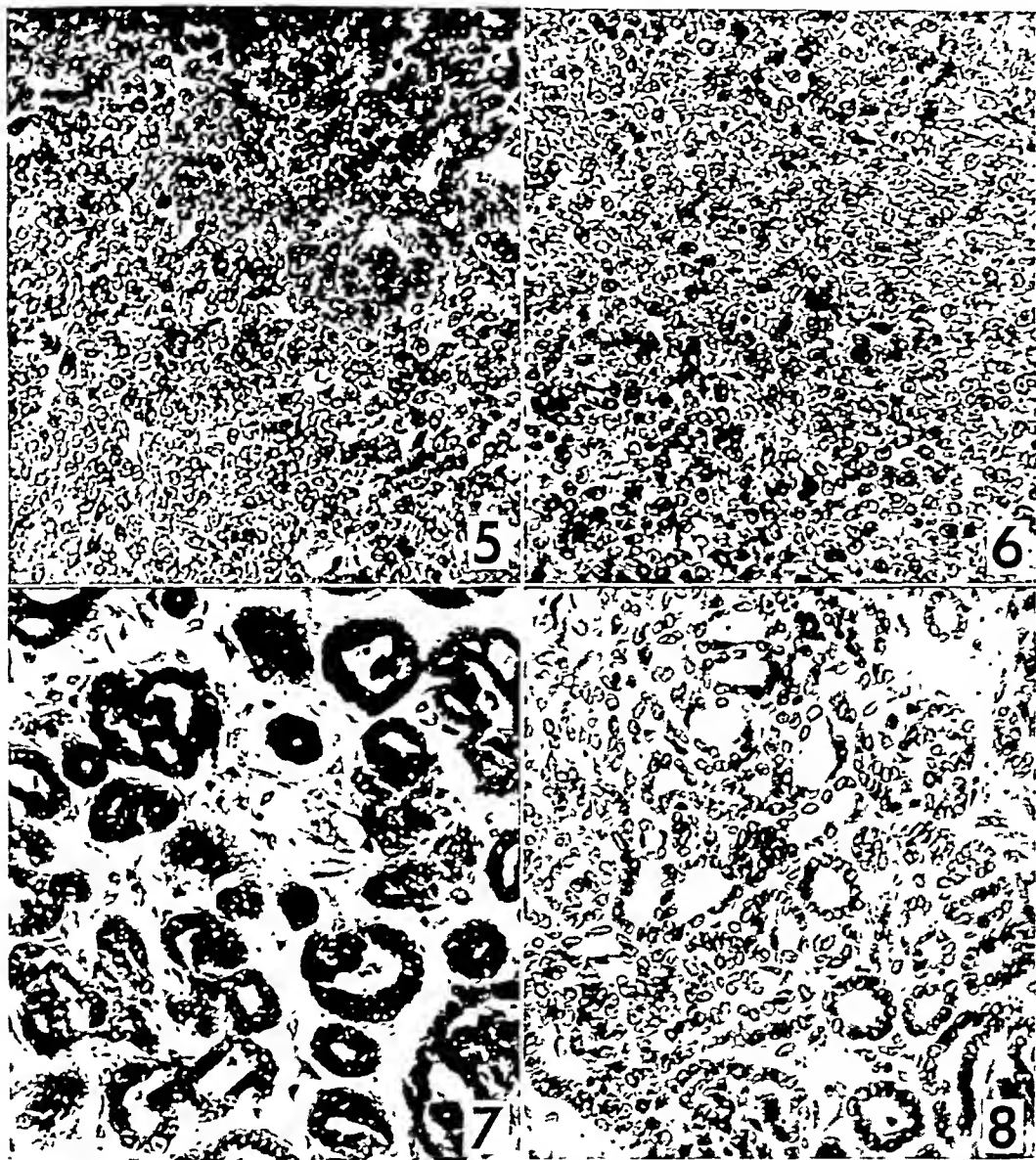


FIG. 5. Case 1 (BE31-3). Section of a metastatic nodule in the kidney showing a further loss of organization (Grade 4).

FIG. 6. Section of homologous anterior chamber transplant of kidney nodule.

FIG. 7. Case 15 (X5728-5). Section of uterine tumor obtained at laparotomy on February 28, 1940, showing a well-organized growth of Grade-2 type. Biopsy specimens obtained on June 1, 1939, November 20, 1939, and April 5, 1940, showed an identical structure.

FIG. 8. Case 15 (X5728-5). Section of autologous subcutaneous transplant made on November 20, 1939. The section was obtained at autopsy, 20 months after transfer, and shows no change in grade with reference to the parent tissue.

All sections were stained with hematoxylin and eosin; all $\times 350$ photographs.

were a mixture of both (Figs. 18 to 24).

Biological Development. A more precise and sensitive index of the developmental state of the tumors was derived from a study of the results of homologous transfer, the criteria being the incidence of takes and the growth rates. Obviously many factors are concerned in determining the incidence of takes. Some are extrinsic, such as faults in transplantation technique, infection, and so on; others are

intrinsic but do not reflect the degree of tumor development, e.g., the amount of stroma, of desmoplastic reaction, or of necrotic tissue included in the fragments used for transfer. Accordingly, in the interpretation of results, more significance has been placed on variations in growth rate than on variations in incidence of takes.

The incidence of takes and the growth rate are shown in Tables 3 and 4. It is immedi-

TABLE 3.

THE INCIDENCE OF TAKES ON HOMOLOGOUS TRANSFER OF TUMOR TISSUE OBTAINED AT VARIOUS LAPAROTOMY EXAMINATIONS AND AT AUTOPSY

Case No.	Animal No.	Tissue from Laparotomy					Tissue from Autopsy %
		First %	Second %	Third %	Fourth %	Fifth %	
1	BE31-3						89(17)*
2	D183-4						
3	D183-5	50					90(21)
4	HA550-2			80(6)	92(22)		40(26)
5	HA586-4					50(29)	60(36)
6	MA13-1	40					
7	MMA10-2	20		60(13)			96(22)
8	X383-3	30					90(16)
9	X1605		25(15)	20(20)			
10	X1800-2	40	100(6)	100(8)			95(20)
11	X2332-7	60					94(12)
12	X2673-6	25		40(6)			95(11)
13	X2678-7	30	100(6)				100(7)
14	X4089-2	75					100(24)
15	X5728-5	15	25(5)		25(10)		100(25)
16	X6101		100(21)				95(21)
17	X6365-2	30		60(6)	50(11)		90(12)
18	X7634-3	100		30(5)			20(23)

* Figures in parentheses refer to the interval in months since the first laparotomy.

TABLE 4.

GROWTH RATES OF HOMOLOGOUS TRANSPLANTS DERIVED FROM TUMOR TISSUE OBTAINED AT VARIOUS LAPAROTOMY EXAMINATIONS AND AT AUTOPSY

Case No.	Animal No.	Time Required for Growth to 0.25 cm. in Diameter Tissue from Laparotomy					Tissue from Autopsy (Days)
		First (Days)	Second (Days)	Third (Days)	Fourth (Days)	Fifth (Days)	
1	BE31-3						10(17)*
2	D183-4						
3	D183-5	150					11(21)
4	HA550-2			50(6)	14(22)		45(26)
5	HA586-4					49(29)	20(36)
6	MA13-1	140					
7	MMA10-2	139		67(13)			13(22)
8	X383-3	120					10(16)
9	X1605		60(15)	52(20)			
10	X1800-2	98	83(6)	75(8)			7(20)
11	X2332-7	84					13(12)
12	X2673-6	107		94(6)			5(11)
13	X2678-7	58	30(6)				13(7)
14	X4089-2	75					40(24)
15	X5728-5	89	70(5)		70(10)		12(25)
16	X6101		15(21)				15(21)
17	X6365-2	100		54(6)	20(11)		10(12)
18	X7634-3	86		85(5)			69(23)

* Figures in parentheses refer to the intervals in months since the first laparotomy.

ately apparent that the tumors were not constant in biological behavior. Moreover, in most, the change in behavior was progressively in one direction—the incidence of takes and the growth rate increasing with the age of the tumor. For example, in case 12, the incidence of takes from successive transfers throughout the course of the tumor was 25 per cent, 40 per cent, and 95 per cent; and the growth rate of the respective transplants, determined by the time required to attain a diameter of 0.25 cm., was 107 days, 94 days, and 5 days. It is clear, therefore, that the biological attributes characteristic of a fully evolved tumor are not present at its inception; on the contrary, these attributes are acquired gradually incident to a process of development.

The degree of development was only partially reflected in morphological appearance. Evidence that a developmental process was operative in the changing tumor morphology is given in Table 2 and a comparison with Tables 3 and 4 shows a gross relationship between anatomical and biological progress in individual cases. Extreme changes in biological behavior were generally associated with an advance in tumor grade; but other significant developments were not attended by concomitant or commensurate histological alterations. In some instances (e.g., case 8) the morphology of the tumor remained constant throughout its course and complete development to autonomy occurred without change of grade while in others (e.g., case 18) an advance in grade was not accompanied by significant changes in biological properties.

Case 4 is of particular interest, for, without change of grade, there was a reversion from a rapid growth rate at the 4th laparotomy to a relatively slow growth rate at the time of autopsy, four months later. Reference to Table 2 shows that, during the interim, a second focus of neoplasia in the vaginal wall attained autonomy and metastasized. The only other instance of metastasis of a second tumor during the course of the fundic growth was also one of carcinoma of the vaginal wall (case 18), and it may be significant that here again the biological properties of the tumor

were not consistent either with the grade or the period of residence in the uterus.

Development of the tumor, either morphologically or biologically, apparently entailed continued residence in the primary host. On transfer to normal animals (Table 5), the morphological grade of the tumor persisted and no advance occurred with the passage of time. In like manner, the incidence of takes and the growth rate remained unchanged irrespective of the length of time the tumor was carried in normal animals. In many instances, tumor tissue obtained at the first laparotomy was carried by serial transfer in normal animals without any change whatsoever in morphology or in biological behavior for periods of time considerably in excess of that required for complete autonomous development in the primary host. It would seem, therefore, that development of the tumor was dependent on factors resident in the primary host and that such factors were not present in normal animals.

DEVELOPMENT OF AUTOLOGOUS TRANSPLANTS

Some indication of the complexity of the factors concerned in tumor development was obtained from a study of autologous transplants. Autologous transfers were performed primarily to study tumor development in the primary host at sites other than the organ of origin, and, for this purpose, the subcutaneous tissue near the laparotomy incision and the anterior chamber of the eye were selected. The fate of the transplants at these sites is shown in relation to morphological grade in Table 6; in Table 7, the grades of the various autologous transplants, the primary tumor, and the metastasis as determined at autopsy, are compared.

It is apparent from these data that the factors concerned in tumor development were not localized in the uterus, for development occurred in as remote and diverse regions as the subcutaneous space and the anterior chamber of the eye. Although a systemic distribution is suggested, the action of the factors was more pronounced in the subcutaneous space than in the eye. Approximately 70 per cent of the subcutaneous transplants

TABLE 5.

A COMPARISON BETWEEN THE GRADE OF THE TUMOR TISSUE USED FOR TRANSFER AND
THE GRADE OF THE HOMOLOGOUS TRANSPLANT

Case No.	Animal No.	Tissue from Laparotomy										Tissue from Autopsy		
		First		Second		Third		Fourth		Fifth		Prim. Tumor	Homo. Trans.	Homo. Metas- tasis
		Tumor	Homo. Trans.	Tumor	Homo. Trans.	Tumor	Homo. Trans.	Tumor	Homo. Trans.	Tumor	Homo. Trans.			
1	BE31-3											3	3	4
2	D183-4													
3	D183-5	2	2									3	3	
4	HA550-2					2	2	3	3			3	3	
5	HA586-4									2	2	2	2	
6	MA13-1	2	2											
7	MMA10-2	2	2			2	2					3	3	4
8	X383-3	2	2									2	2	2
9	X1605			2	2	2	2							
10	X1800-2	2	2	2	2	2	2					4	4	4
11	X2332-7	2	2											4
12	X2673-6	2	2			2	2					3	3	
13	X2678-7	2	2	3	3							4	4	4
14	X4089-2	2	2									2	2	
15	X5728-5	2	2	2	2			2	2			3	3	4
16	X6101			2	2							2	2	4
17	X6365-2	2	2			2	2	3	3			3	3	
18	X7634-3	2	2			2	2					3	3	

TABLE 6.

THE DEVELOPMENT OF HISTOLOGICAL GRADE IN AUTOLOGOUS TUMOR TISSUE TRANSPLANTS DURING THE COURSE OF
DIFFERENT LAPAROTOMY EXAMINATIONS

Case No.	Animal No.	Prim. Tumor	First Laparotomy		Aut.	Second Laparotomy			Third Laparotomy		Fourth Laparotomy	
			Biop.	Autoplant Biop.		Prim. Tumor	Biop.	Autoplant Aut.	Prim. Tumor	Autoplant Autopsy	Prim. Tumor	Autoplant Autopsy
1	BE31-3	2			3(17)*							
2	D183-4	2	3(5)		4(10)							
3	D183-5	2			4(21)							
4	HA550-2											
5	HA586-4											
6	MA13-1	2	2(11)	3(21)	3(21)						3	3(4)
7	MMA10-2	2	2(3)		†Sarc(22)	2		Sarc(19)				
		2			†E2(22)							
8	X383-3	2			2(16)							
		2			E2(16)							
9	X1605					2		2(3)				
						2		E2(3)				
10	X1800-2	2			E3(18)			3(14)		4(12)		
11	X2332-7	2	3(3)		4(12)							
		2			E3(12)							
12	X2673-6	2	2(4)		2(11)							
		2			E2(11)							
13	X2678-7	2			E2(7)	3		4(1)				
14	X4089-2	2			2(24)							
15	X5728-5	2			E2(25)	2	2(3)	2(20)		4(17)		
16	X6101	2			4(21)							
17	X6365-2	2	2(4)		4(12)	2		4(9)				
		2			E2(12)							
18	N7634-3	2	2(3)		2(22)	2		2(19)				

* Figures in parentheses represent the interval in months between autologous transfer and removal of tissue for histological study.

† Sarc = Sarcoma.

‡ E = Autologous eye transplant. Other autologous transplants were made in the subcutaneous tissues of the belly wall.

TABLE 7.

A COMPARISON OF THE VARIOUS AUTOLOGOUS TRANSPLANTS, THE PRIMARY TUMOR, AND METASTASES BASED ON THE HISTOLOGICAL GRADE OF SPECIMENS OBTAINED AT AUTOPSY

Case No.	Animal No.	Grade at Autopsy						Autopsy Primary Tumor	Metastasis
		First		Laparotomy Second		Third Auto-plant S-c	Fourth Auto-plant S-c		
		Autoplant S-c	Eye	Autoplant S-c	Eye				
1	BE31-3	3						3	4
2	D183-4	4						3	3
3	D183-5	4						3	4
4	HA550-2						3	3	
5	HA586-4							2	
6	MA13-1	3						2	
7	MMA10-2	Sarc.	2	Sarc.				3	4
8	X383-3	2	2					2	2
9	X1605			2	2			2	
10	X1800-2		3	3		4		4	4
11	X2332-7	4	3					4	4
12	X2673-6	2	2					3	3
13	X2678-7		2	4				4	4
14	X4089-2	2						3	
15	X5728-5		2	2		4		3	4
16	X6101	4						2	4
17	X6365-2	4	2	4				3	4
18	X7634-3	2		2				3	

showed an advance in grade in contrast to less than 20 per cent of the anterior-chamber grafts. Moreover, the degree of advance was much greater. In fact, in a number of instances (cases 2, 3, 6, 16, and 17), the grade of the subcutaneous transplant was higher than that of the primary uterine tumor. This was extreme in case 16 in which the morphology of the metastases was identical with that of the subcutaneous transplant and in sharp contrast to the well-organized primary tumor, suggesting that the metastases were actually derived from the transplant rather than from the uterus (Figs. 13 to 17).

The irregular action or distribution of the factors concerned in tumor development is well illustrated in case 15 (Figs. 7 to 12). At death, tumor tissue of all grades was present in the one animal. The anterior-chamber transplant of the first laparotomy and the subcutaneous transplant of the second were both of Grade 2. The primary tumor in the uterus was of Grade 3 while the subcutaneous transplant of the third laparotomy and the metastases were of Grade 4. It should be noted that the two subcutaneous transplants lie less than 3 cm. apart, one on either side of the laparotomy incision, yet one remained a Grade-2 tumor while the other advanced to

Grade 4. The growth from which these two transplants were derived was in a Grade-2 stage at both transfers, and the transplanted tissues differed from one another only by the fact that one had resided in the uterus three months longer than the other. A somewhat comparable circumstance is found in case 10. Here both the second and third autologous transfers were derived from a Grade-2 primary tumor; yet the former had advanced to Grade 3 at the time of autopsy while the latter, obtained after a two months longer residence in the uterus, had progressed to Grade 4. The point is of obvious interest in the present context, but the available data is manifestly insufficient for clarification or further discussion.

It is true that the distribution of tumor in case 15 was in part artificially produced and not one likely to be encountered in practice. Yet a question of practical interest arises as to the nature of the prognosis to be offered, if the problem had confronted a surgical pathologist. On a basis of morphology, the prognosis would necessarily vary depending on the region selected by the surgeon for biopsy and, if several sites were chosen, the pathological prophecies would cover the whole range from good to horrible on the

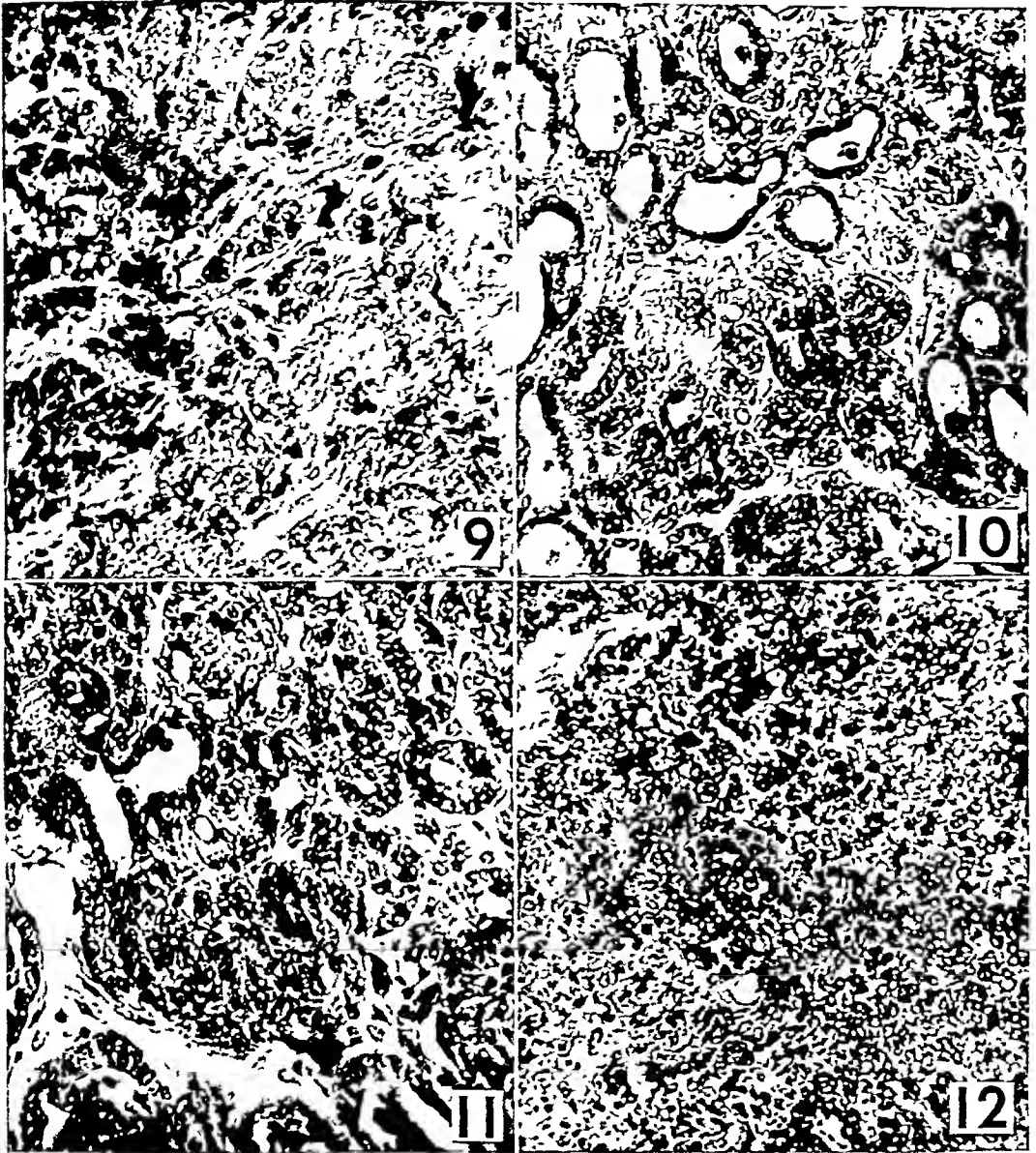


FIG. 9. Case 15 (X5728-5). Section of autologous subcutaneous transplant made on February 28, 1940. This section was obtained at autopsy seventeen months after transfer and shows a marked loss of organization in comparison to the parent tissue (Grade 4).

FIG. 11. Case 15 (X5728-5). Section of uterine tumor obtained at autopsy showing a loss of organization when compared with previous biopsies but of a lesser degree than characterized the autologous transplant of February 28, 1940. (Grade 3).

FIG. 10. Case 15 (X5728-5). Section of autologous anterior chamber transplant made June 1, 1939. The section was obtained at autopsy, twenty-five months after transfer, and shows no change in organizational grade (Grade 2).

FIG. 12. Case 15 (X5728-5). Section of metastasis in mediastinal lymph node. The growth is less organized than that of the primary tumor in the uterus and is comparable to the subcutaneous transplant of February 28, 1940. (Grade 4).

All sections were stained with hematoxylin and eosin; all $\times 350$ photographs.

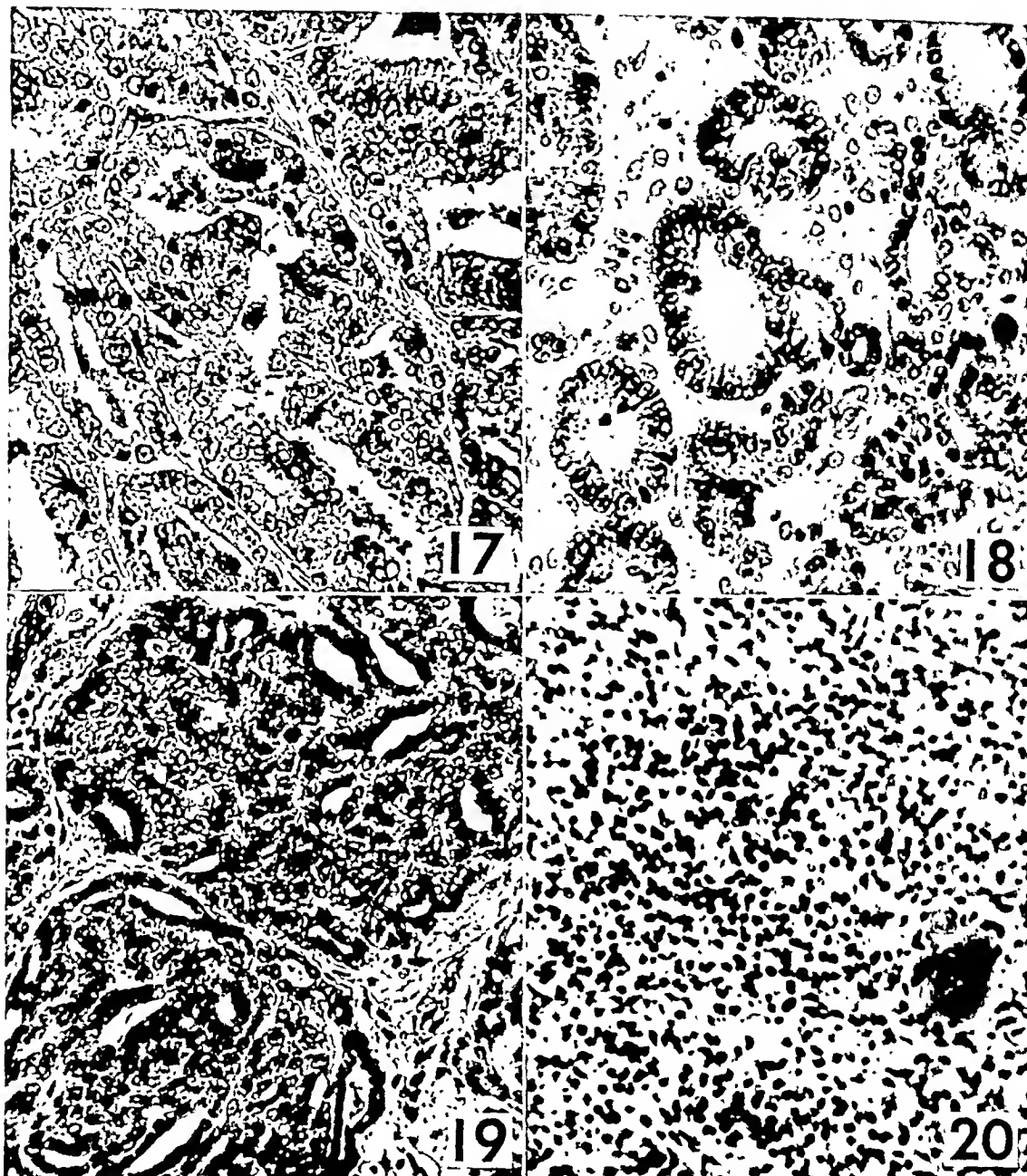


FIG. 17. Case 16 (X6101). Section of co-incident adenocarcinoma of breast.

FIG. 18. Case 7 (MMA10-2). Section of uterine tumor obtained at laparotomy on November 18, 1939, showing a Grade 2 growth. Biopsy specimens obtained on February 29, 1940, and December 5, 1940, showed an identical structure.

FIG. 19. Case 7 (MMA10-2). Section of autologous anterior chamber transplant made on November 18, 1939. The section was obtained at autopsy, twenty-two months after transfer and shows no change in organization with reference to the parent tissue (Grade 2).

FIG. 20. Case 7 (MMA10-2). Section of autologous subcutaneous transplant made on November 18, 1939. Like the previous section this was obtained at autopsy twenty-two months after transfer but, in sharp contrast, shows a complete alteration in structure with replacement of the adenocarcinoma by a sarcoma.

All section were stained with hematoxylin and eosin; all $\times 350$ photographs.

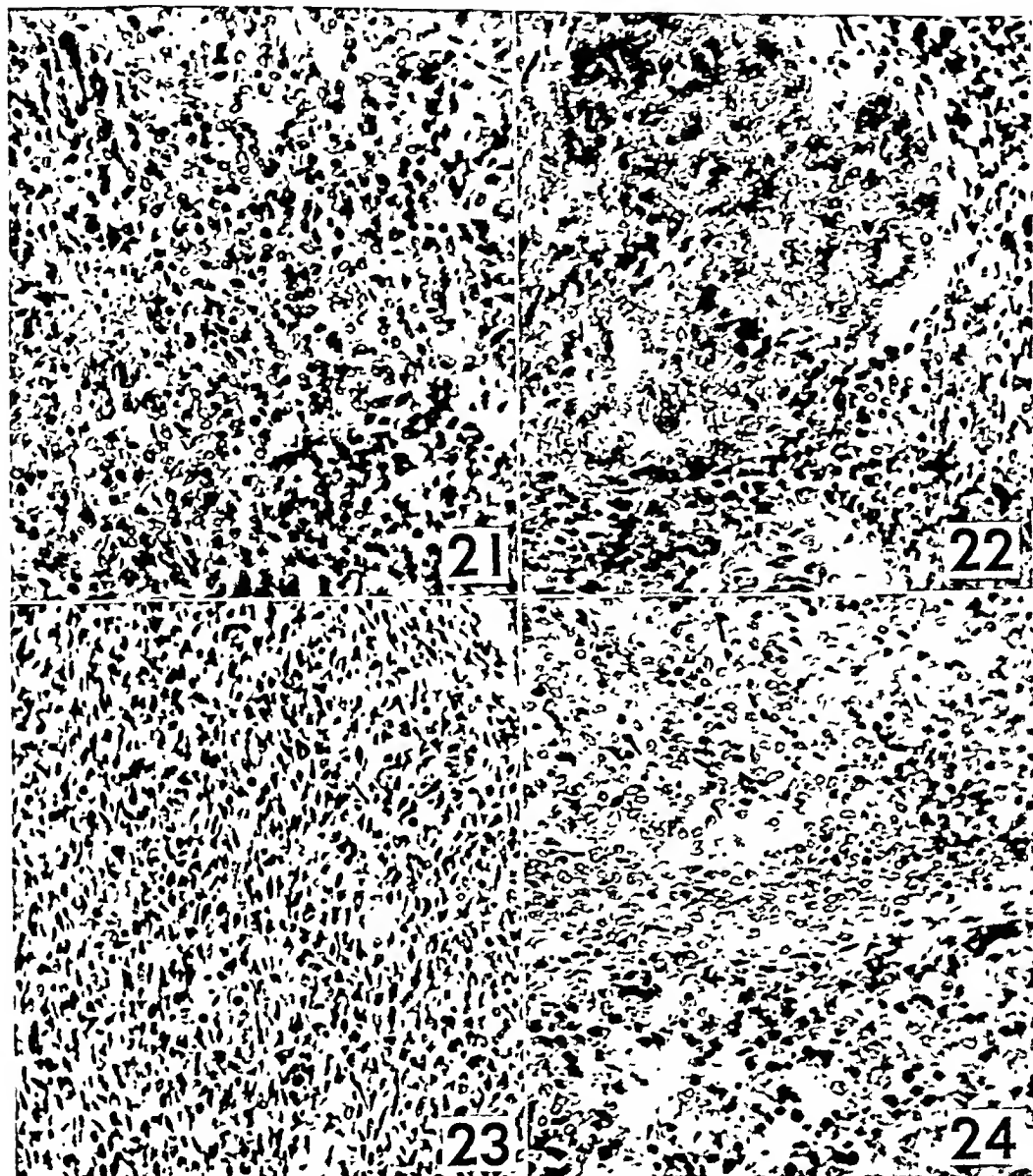


FIG. 21. Case 7 (MMA10-2). Section of uterine tumor obtained at autopsy showing an area of Grade-3 adenocarcinoma.

FIG. 22. Case 7 (MMA10-2). Section of uterine tumor obtained at autopsy showing an area containing both adenosarcoma and carcinoma.

FIG. 23. Case 7 (MMA10-2). Section of uterine tumor obtained at autopsy showing an area in which the carcinoma has been completely replaced by sarcoma.

FIG. 24. Case 7 (MMA10-2). Section of metastatic nodule in diaphragm showing a Grade-4 carcinoma in the lower half and a sarcoma in the upper.

All sections were stained with hematoxylin and eosin; all $\times 350$ photographs.

appear to be in disagreement with those obtained in mouse-tumor transplant experiments. The disagreement, however, is not actual but stems from differences in material, methods, and definitions. The transplantation of a spontaneous mouse tumor is generally effected from tissue obtained after the animal has been killed rather than from biopsy material. Moreover, transfer is usually performed when the tumor is first discovered rather than at the end of its developmental course. Mice of the same inbred strain are used as hosts and takes occur even if the growth is in an early developmental stage. In contrast, transfer to alien strains fails, a situation actually analogous to that found in the transfer of early rabbit tumors and the apparent lack of conformity arises from the use of genetically different animals as experimental hosts. The selection of recipients in homologous rabbit transfers is based on remoteness of relationship while in mice these are selected on a basis of consanguinity. Accordingly, autologous transfer in rabbits and transfer to the strain of origin in mice (mouse homologous transfer) possess the same significance. In like manner, homologous transfer in rabbits is biologically comparable to transfer to an alien strain in mice. The results obtained in the two species are thus fundamentally the same.

In contrast to the stability of rabbit tumors under homologous transfer, mouse tumors carried serially in the strain of origin occasionally undergo further development. The probable explanation lies in the fact that with continued passage in animals of the same genetic constitution as the original donor, the tumor eventually comes to reside in an individual possessing the essential developmental factors. Transfer of the altered tumor to an alien strain then results in takes.

The transplantability of spontaneous mouse tumors has been under study in this laboratory using the same methods employed in the present investigation, and the results are essentially the same. The autologous transfer of early mouse tumors or the homologous to members of the strain of origin is invariably successful whereas transfer to alien strains or to guinea pigs fails. On the other hand, after complete development as determined by me-

tastasis, transplantation to alien strains or to guinea pigs is readily effected.

An identical situation obtains with respect to rabbit tumors other than those of the uterine fundus. A comparable investigation of human tumors with autologous and homologous transfers is obviously impossible. But considerable information can be obtained from the heterologous transplantation of successive biopsy specimens secured at intervals throughout the period of development. An opportunity for several such experiments has been made available and the results indicate a complete parallelism with the tumors of rabbits and mice. That is, the tumors are not transplantable to guinea pigs during early stages of development but become transplantable during their terminal stages, suggesting the occurrence of the same phases of dependency and autonomy that characterize the tumors of other species.

The conception of cancer as a developmental process dependent on specific factors rather than as an abrupt and complete metamorphosis yields inferences suggesting new lines of investigation. A natural division of the problem into two separately approachable parts is immediately implied: the initiation of neoplasia and the development of the neoplastic focus to cancer. There is actually very little evidence to suggest that the two processes are etiologically related and much to indicate that they are referable to the operation of quite distinct sets of factors. Although the factors concerned in the initiation of neoplasia may be extrinsic as well as intrinsic in nature (chronic irritation, possibly even viruses) there is nothing to show that their continued action is concerned in the subsequent development of the focus to cancer. Neoplasia is an extremely frequent pathological lesion and constitutes an almost constant finding in carefully executed autopsies. In contrast, cancer is comparatively rare. Accordingly, it would appear that the factors concerned in the initiation of neoplasia were much more widely distributed than those concerned in the conversion of the neoplastic focus to cancer. Moreover, from a humanitarian point of view the latter factors would seem to be much the more important.

Very little information is available regarding the nature of the factors concerned in the development of the neoplastic focus and the present study does no more than to suggest their existence and to illustrate their complexity. They are apparently intrinsic in nature, systemically distributed, and not a part of the constitutional make-up of a normal animal. Development to cancer will occur in the subcutaneous space and in the eye as well as in the uterus of a tumor-bearing animal showing that the factors are generalized, not localized about the primary neoplastic focus. Development occurs with greater regularity and rapidity in the subcutaneous space than

in the eye suggesting a variation in the concentration or activity of the factors. It is possible that this may relate to the fact that transplants in the subcutaneous space were necessarily placed in close proximity to breast tissue and that the endometrium and breast may have more in common than the endometrium and the eye. It is suggestive that foci of neoplasia in various stages of development are constantly present in the breasts of animals bearing uterine tumors. Moreover, in one case in which a subcutaneous transplant was placed in proximity to a breast cancer, the rate and degree of development were much greater than in the uterus.

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ELECTROPHORETIC STUDIES ON THE PLASMA PROTEINS OF PATIENTS WITH NEOPLASTIC DISEASE

*I. Gastric Cancer**

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AMONG the metabolic abnormalities found in patients with gastric cancer, a deficiency in the plasma albumin is outstanding.² Even when a strongly positive nitrogen balance is maintained (by a high intake of protein and protein hydrolysate) the plasma albumin level does not rise.⁷ A second abnormality is revealed by a comparison of the albumin values obtained by the Howe and electrophoretic methods.¹⁰ Whereas in normal subjects the α -globulins are soluble in sodium sulfate and are included in the Howe albumin fraction, the α -globulins of patients with gastric cancer frequently show the insolubility in sodium sulfate that has been found in cases of hepatic dysfunction.¹³ When such patients are treated with protein hydrolysate, the α -globulins become more soluble, and the Howe method shows an apparent increase in albumin which is not substantiated by electrophoretic analysis.¹⁰ Consequently, only the electrophoretic albumin values are sufficiently accurate to be used in albumin regeneration studies.

In this paper the results of the electrophoretic analyses made on the nine patients studied by Homburger and Young are reported in more detail. A group of normal subjects, an additional series of patients with gastric ulcer and gastric cancer, and four patients whose gastric tumors had been removed five years previously are also included.

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* These studies were made possible through the co-operation of Dr. G. T. Pack and Dr. G. McNeer and the staff of the Gastric Service of Memorial Hospital. Some of the expenses of the investigation were defrayed by a grant from the James Foundation of New York, Inc.

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Received for publication, December 15, 1947.

METHODS

Blood samples were taken from all subjects in the postabsorptive state with sodium citrate as anticoagulant. The total plasma protein was determined by Kjeldahl analysis and corrected for non-protein nitrogen. The plasma was analyzed electrophoretically in veronal-citrate buffer at pH 8.6 and ionic strength 0.010. A detailed description of the techniques used has been given by Petermann, Young and Hogness. Since values for the various protein components given in percentages of total protein may be quite misleading when the total protein concentration is abnormal, the concentration of each electrophoretic component is here reported in grams per 100 cc. of plasma.

RESULTS

The concentrations of the various electrophoretic components in the plasma of normal subjects (healthy young adults of both sexes) are shown in Fig. 1. For each component the normal range is indicated by the shaded area, and the normal average by the line across the shaded portion. The values found agree with those reported in the literature for this protein concentration, pH, and ionic strength.³

The albumin and globulin concentrations found in six patients with gastric ulcer are indicated by the crosses in Fig. 1. Their chief abnormality is a low plasma albumin. In two cases the α_1 -globulin is increased; the amounts of the other globulin fractions found are quite normal.

The values found for twenty-five patients with gastric cancer are marked by dots on Fig. 1. The albumin concentrations are all far below the lowest normal value. The α_1 -globulin levels are high, falling in the upper part of the normal range or above it. The

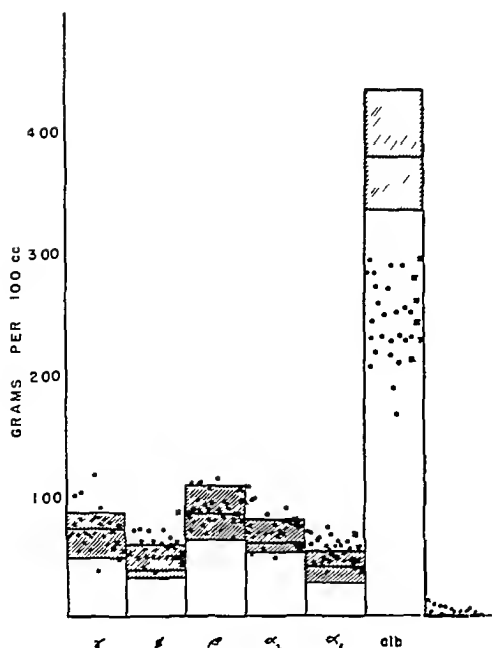


FIG. 1. The concentrations of the plasma protein components in normal subjects, patients with gastric ulcer, and patients with gastric cancer. (See text). • = albumin; x = gastric ulcer.

values for the α_2 -globulin are also increased, although not so markedly as are the α_1 -globulin. The fibrinogen concentration is increased, often to almost twice the normal average. The β -globulin is normal, and so are most of the γ -globulin values. In many of these plasmas a small boundary is seen ahead of the albumin; this may represent the lipoprotein described by Armstrong et al. Typical diagrams obtained on the plasma of normal subjects and of patients with ulcer and gastric cancer are shown in Fig. 2.

As part of the metabolic studies of Homburger and Young, the plasma proteins of nine patients on high protein intakes were analyzed at weekly intervals. Some of the results are given in Table 1. When the gastric tumor was still present, as in patients No. 7, 9, 10, 11, and 13, all the abnormalities persisted. When the tumor had been removed, as in patients No. 4, 5, and 6, the α -globulins and fibrinogen returned to normal levels in a few weeks. By contrast, the restoration of

plasma albumin was very slow; that it can take place eventually, however, is shown by the nearly normal values obtained from the five-year survivors. The primary gastric tumor of patient No. 12 had been removed, but it was felt that lymphatic metastases persisted. It is interesting to note that his α -globulin and fibrinogen concentrations became normal in eleven days, while the albumin remained low even after 108 days on a high-protein regimen. The histories of these patients have been reported elsewhere.⁷

DISCUSSION

None of the abnormalities found in these analyses is characteristic of cancer in general or of gastric cancer in particular. The low plasma albumin is found in many malnourished patients. The striking difference in patients with gastric cancer lies in their failure to regenerate plasma albumin while in strongly positive nitrogen balance.⁷ Low albumin and high α -globulin levels have been reported in twenty-three cases of carcinoma of various types.¹² Increases in the α -globulins are found in many wasting diseases where

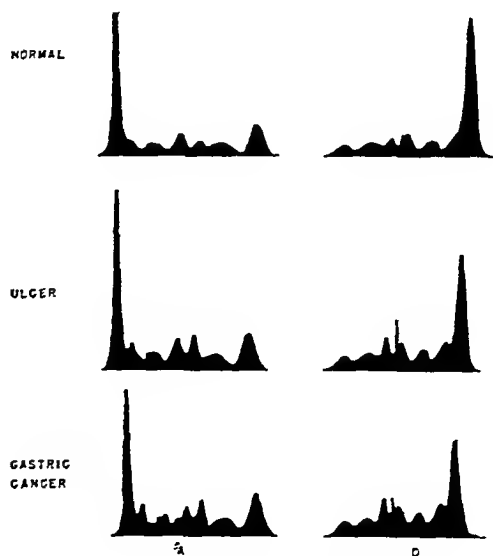


FIG. 2. Representative electrophoretic patterns obtained on the plasma of normal subjects, patients with gastric ulcer, and patients with gastric cancer. "A" denotes the ascending boundary and "D," the descending boundary.

tissue breakdown is taking place.^{4, 11, 12} The increase in fibrinogen is of the same magnitude as that found by chemical methods.^{1, 6} A similar rise in fibrinogen is often found in association with a moderate degree of liver damage.⁵

It may therefore be concluded that electrophoretic analysis of the plasma of patients with gastric cancer at pH 8.6 in veronal-citrate buffer gives results that are characteristic of wasting disease in general but are not

specific for cancer. A similar conclusion has been reached by Luetscher, who states that the plasma electrophoretic pattern "has proved to be characteristic not of the specific disease but of the host's reaction to infection and injury." Analyses at pH 4.0, on the other hand, do show definite changes in the plasma-protein pattern which may prove to be characteristic of neoplastic disease. These studies are reported in the second paper of this series.⁹

TABLE I

THE EFFECT OF A HIGH PROTEIN INTAKE ON THE PLASMA PROTEINS OF PATIENTS WITH GASTRIC CANCER

Diagnosis	Patient No.	Days on Regimen	Plasma Proteins in Grams per 100 cc.						
			Total	Alb.	α_1	α_2	β	ρ	γ
	Normal Av.		7.04	3.79	0.41	0.61	0.86	0.39	0.74
	Normal Range		6.31-7.97	3.35-4.35	0.28-0.62	0.53-0.81	0.63-1.18	0.32-0.59	0.49-0.87
Gastric Cancer-Inoperable	7	0	6.13	2.88	0.44	0.66	0.88	0.59	0.69
		14	6.81	2.71	0.54	0.78	1.09	0.75	0.93
	9	0	7.00	2.93	0.69	0.97	1.11	0.60	0.70
		14	5.33	2.00	0.66	0.72	0.90	0.43	0.63
	10	0	6.79	2.72	0.63	0.79	1.10	0.73	0.82
		12	6.75	2.44	0.72	0.89	1.17	0.72	0.81
		24	6.54	2.30	0.71	0.89	1.10	0.67	0.88
	11	0	6.37	2.41	0.66	0.76	1.11	0.57	0.86
		10	5.80	1.89	0.62	0.63	1.15	0.49	1.02
		15	4.77	1.45	0.57	0.50	1.06	0.34	0.86
	13	0	5.32	2.35	0.46	0.51	0.83	0.49	0.70
		21	6.33	2.86	0.61	0.51	0.96	0.55	0.84
	43	6.78	2.90	0.74	0.46	1.11	0.60	0.96	
	71	5.99	2.24	0.66	0.53	1.05	0.53	0.98	
Tumor Removed but Metastases to Nodes	12	0	6.23	2.51	0.68	0.80	0.90	0.57	0.77
		22	5.88	2.80	0.47	0.46	0.84	0.48	0.83
		52	6.02	2.84	0.46	0.54	0.91	0.40	0.88
		60	5.48	2.60	0.42	0.48	0.81	0.37	0.81
		108	5.11	2.42	0.43	0.46	0.71	0.33	0.76
Tumor Removed No Metastases	4	0	5.76	2.58	0.49	0.61	0.88	0.50	0.70
		6	6.07	2.37	0.57	0.90	0.97	0.59	0.67
		11	5.25	1.99	0.48	0.74	0.91	0.45	0.68
	5	0	6.13	2.07	0.71	0.98	0.89	0.72	0.77
		16	6.24	1.77	0.84	0.89	0.92	0.72	1.10
		85*	5.32	2.34	0.46	0.64	0.70	0.42	0.76
	6	0	5.24	2.18	0.58	0.56	0.76	0.60	0.56
		6	5.77	1.93	0.62	0.65	0.88	0.70	0.99
		11	6.50	2.34	0.59	0.66	1.03	0.69	1.18
		18	6.56	2.61	0.49	0.59	0.98	0.64	1.26
Tumor Removed No Metastases	14	5†	6.99	3.58	0.43	0.71	1.09	0.43	0.75
	15	5†	7.19	3.22	0.48	0.66	1.11	0.48	1.24
	16	6†	6.14	3.21	0.50	0.49	0.90	0.39	0.66
	17	6†	6.05	3.41	0.36	0.59	0.86	0.32	0.52

* Two months on normal diet.

† Years after gastrectomy, on normal diet.

SUMMARY

1. In patients with gastric ulcer the hypoproteinemia is due entirely to a decrease in plasma albumin. The concentrations of the other protein components are normal.

2. Patients with gastric cancer also have a marked decrease in the plasma albumin. Their α -globulin and fibrinogen concentra-

tions are somewhat above the normal level, while the β - and γ -globulins are normal.

3. After the tumor has been removed, the α -globulins and fibrinogen return to normal levels within a few weeks. The increase in albumin, on the other hand, appears to be extremely slow, even in patients maintained in strongly positive nitrogen balance.

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ELECTROPHORETIC STUDIES ON THE PLASMA PROTEINS OF PATIENTS WITH NEOPLASTIC DISEASE

II. *An Acid Protein Present in the Plasma**

MARY L. PETERMANN, PH.D.† and KATHARINE R. HOGNESS, B.SC.

WHEN the plasma proteins of patients with gastric cancer are analyzed electrophoretically in alkaline solution, some of the components are found to be present in abnormal amounts.¹² The decrease in albumin and increases in α -globulins and fibrinogen are similar to those found in many wasting diseases, however, and no abnormality characteristic of cancer can be discerned. The possibility exists, nevertheless, that in other buffers and at different hydrogen ion concentrations, electrophoretic analysis may reveal the presence of some specific change in the plasma-protein patterns of patients with cancer. Since it was found by Luetscher that purified human serum albumin separates into two components at pH 4.0 in acetate buffer, the same pH was chosen for the experiments described in this report.

At pH 4.0 in an acetate-chloride buffer, the plasma albumin and most of the other proteins carry a positive net charge and migrate toward the cathode. In most samples of plasma another small boundary is also seen that moves in the opposite direction; this indicates the presence of a substance that is negatively charged at pH 4.0 and therefore has an isoelectric point much lower than those of the well-known plasma proteins.

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* These studies were made possible through the co-operation of Dr. G. T. Pack and Dr. G. McNeer and the staff of the Gastric Service and Dr. L. F. Craver and the staff of the Medical Service of Memorial Hospital. We are particularly indebted to Dr. F. Homburger and Dr. D. A. Karnofsky of this Institute, Dr. H. Colcher of Goldwater Memorial Hospital, and Dr. T. Almy of New York Hospital for selecting the patients and securing the blood samples. Some of the expenses of this investigation were defrayed by a grant from the James Foundation of New York, Inc.

† Finney-Howell Research Foundation Fellow, 1947-1948.

Received for publication, December 15, 1947.

Since the outstanding characteristic of this material is its acidic nature, it is here referred to as the "acid component." In some types of neoplastic disease the concentration of this substance is significantly increased.

METHODS

Blood samples were taken from all subjects in the postabsorptive state, with sodium citrate as anticoagulant. Total plasma protein was determined by Kjeldahl analysis and corrected for nonprotein nitrogen.

The plasma samples were diluted to a protein concentration of 2.15 per cent with acetate buffer and dialyzed for two days against two lots of buffer. The buffer had an ionic strength of 0.10, and consisted of 0.08 M NaCl, 0.02 M sodium acetate and enough acetic acid to adjust the pH to 4.0. A small precipitate which formed on dialysis was removed by centrifugation.

At the beginning of an electrophoretic experiment the boundary was drawn into the cell to about one-third its length. A potential of 6 volts per centimeter was then applied for 180 minutes. Further details of the techniques used have been given elsewhere.¹⁴

Representative patterns obtained on the plasmas of normal subjects and of patients with gastric cancer are shown in Fig. 1. The arrows indicate the direction of migration from the starting boundary. On the descending side the albumin and globulins move toward the cathode as one broad, asymmetrical boundary that cannot be resolved into individual components. The boundary B is the salt boundary. The acid component gives rise to a boundary A, that migrates anodically with a mobility of -2.7×10^{-5} cm.²/sec./volt.

On the ascending side a very different pat-

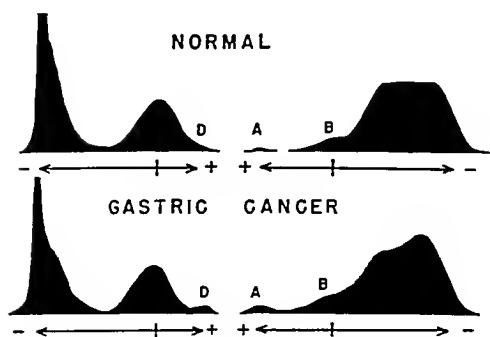


FIG. 1. Representative electrophoretic patterns obtained at pH 4.0 on the plasmas of normal subjects and of patients with gastric cancer. The rising boundaries are on the left, and the falling boundaries on the right.

tern is obtained. A large fraction of the protein remains at the starting boundary, while most of the rest moves toward the cathode. The pronounced differences in form between these boundaries and those on the descending side suggest that, at this pH, complex formation occurs among the various plasma-protein constituents. The acid component shows up here as a boundary D that migrates anodically but never separates completely from the large stationary boundary. The area of the boundary D (which migrates through the protein solution) is always larger than the area of the boundary A (which is moving into a solution of buffer alone).

In calculating the amount of acid component present, this has been assumed to have the same refractive index as the other plasma proteins. On the descending side the per cent of A has been calculated by taking the ratio of its area to that of the total area exclusive of the salt boundary. On the ascending side the per cent of the total area was used in the calculation of D, since the size of the salt boundary could not be determined.

RESULTS AND DISCUSSION

These analyses indicate that the amount of acid component in the plasma is significantly increased in gastric cancer and in cancer of the lung. Some high values were also encountered in lymphatic leukemia and in Hodgkin's disease. The results are sum-

marized in Fig. 2. The samples from the fifteen subjects free of neoplastic disease included plasmas from six normal subjects, four cases of cirrhosis of the liver, two of familial idiopathic dysproteinemia,⁴ one of chronic pancreatitis, and one of severe weight loss with no evidence of organic disease; there was also one placental serum. The amounts of A found never exceeded 100 mg. per cent. The amount of D always appeared to be somewhat larger, with eight values below 100 mg. per cent, five between 100 and 110, one of 140 and one of 170 mg. per cent. The two highest values were obtained on laboratory personnel. Of these, one had enlarged adenoids and a cervical adenitis associated with a history of repeated upper respiratory infections. The other had enlarged cervical nodes which were diagnosed on a biopsy specimen as hyperplastic lymph nodes. These same two subjects were the only cases in which the average of A and D was over 100 mg. per cent.

In six patients with gastric ulcer, the amount of A was similar to that found in the control group—never over 70 mg. per cent. The values for D, on the other hand, were lower than those found in many of the controls; levels higher than 80 mg. per cent were never encountered.

Of the entire group of twenty-one subjects free of neoplastic disease only the two with enlarged nodes had more than 100 mg. per cent (110 and 115) average concentration of A and D.

Of the sixteen patients with gastric cancer, only five had less than 100 mg. per cent of A; only one had less than 100 mg. per cent of D; and three had less than 100 mg. per cent average acid component. Of these three, two had widespread, inoperable lesions. The third, the only patient in this group with less than 50 mg. per cent of A, and less than 100 mg. per cent of D, had a very small tumor.

Three patients examined within three months after the removal of the tumor still had a somewhat increased amount of this substance; but a group of six who had survived gastrectomy for cancer for more than one year all had normal values, averaging less than 100 mg. per cent.

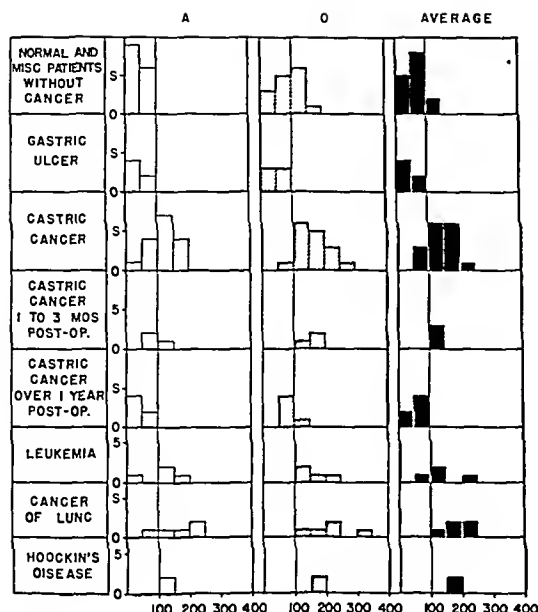


FIG. 2. The distribution of the acid component in the plasma of normal subjects and patients. The ordinate indicates the number of subjects in each group, while the abscissa shows the amount of acid component in mg. per 100 cc. of plasma. The columns represent the number of subjects of each type whose plasma contained 0-50, 50-100, etc., mg. per 100 cc. of acid component. The unshaded columns represent the acid component calculated from the A boundary; the shaded columns represent results obtained from the D boundary, and the solid columns show the distribution of the averages of A and D.

Five patients with cancer of the lung all had more than 100 mg. per cent average acid component. The substance was also increased in three out of four cases of lymphatic leukemia and in two cases of Hodgkin's disease.

The precise nature of the acid substance that has this distinctive mobility at pH 4.0 has not yet been determined. It is soluble in 55 per cent ammonium sulfate, and remains in solution under the conditions described by Pillemer and Hutchinson for the precipitation of the globulin fraction of plasma. These are a methanol concentration of 42.5 per cent, pH 6.7-6.9, ionic strength 0.03, and 0°. When the ammonium sulfate and methanol filtrates were examined electrophoreti-

cally at pH 8.6 in veronal-citrate buffer, ionic strength 0.10, only albumin and α -globulins were found. Many of the whole plasma samples have also been analyzed electrophoretically at pH 8.6; the results of these analyses have been reported in other papers of this series.^{12, 13} In general, the patients with the highest concentrations of acid component also showed the largest increases in α -globulins.

Small amounts of the material have been isolated electrophoretically. It shows the ultraviolet absorption spectrum characteristic of proteins, and gives a metachromatic reaction with toluidine blue similar to that given by high molecular weight sulfuric acid esters.¹⁸ Preliminary studies by Dr. Aaron Bendich of this laboratory have shown that it contains aminosugar and additional reducing sugar whose properties suggest the presence of uronic acid. That the acid component is not hyaluronic acid, however, has been demonstrated in two ways. First, as mentioned above, when albumin fractions containing considerable amounts of acid component were analyzed electrophoretically at pH 8.6, no substance more highly charged than albumin was seen. Hyaluronic acid has a much higher mobility than albumin in alkaline solution. Second, hyaluronic acid prepared from human umbilical cord by the method of Haas was added to normal plasma in amount equal to 5 per cent of the total protein concentration. When the mixture was dialyzed against the pH 4.0 buffer, a heavy precipitate appeared. After this precipitate had been removed by centrifugation, electrophoretic analysis showed no increase in the concentration of acid component in the plasma.

Another acid protein is fetuin, so called by Pedersen because it is found chiefly in the plasma of the fetus and new-born animal. Fetuin differs from the acid component in that it is insoluble in half-saturated ammonium sulfate and has a mobility of about 1.0×10^{-5} cm²/volt/sec. at pH 4.0. The one sample of human placental serum which was analyzed electrophoretically at pH 4.0 was found to contain no measurable amount of acid component.

The glycoprotein, haptoglobin, whose concentration is greatly increased in the plasma of patients with cancer, tuberculosis, and other chronic diseases,³ is precipitated by 55 per cent saturated ammonium sulfate,⁵ whereas the acid component remains in solution, as described earlier.

Other workers^{8, 17} have found increased amounts of carbohydrate in the plasma of patients with various types of cancer.

There are, however, one or more acid mucoproteins in plasma that resemble the acid component closely in many of their properties. Mayer has isolated the substance responsible for the distinctive polarographic curve given by the serum of patients with cancer. The material was heat stable and soluble in sulfosalicylic acid; its isoelectric point (point of minimum solubility) was at pH 3.4. The substance contained 10 to 11 per cent of nitrogen and 17 to 18 per cent of carbohydrate, of which half was glucosamine. It gave positive biuret, Millon, and xanthoproteic tests, and contained sulfur. The yield from normal serum was 14 mg. per cent, while more than twice this amount was obtained from the serum of patients with cancer. A similar substance has been prepared from ox serum by Rimington.

Winzler^{20, 21, 22} has fractionated the heat-stable plasma proteins with ammonium sulfate and obtained a material called a "mucolipoprotein." Its isoelectric point is at pH 3.7 to 3.8; at pH 8.5, it separates into at least two components, of mobility -5.8 and -6.0×10^{-5} cm.²/volt/sec. It contains 18 per cent glucosamine, 20 per cent saponifiable lipid, and 1.5 per cent sulfur.

A more extensive study of the occurrence of the acid component in other types of cancer and wasting disease awaits its estimation

by a quantitative chemical method that will be less laborious than electrophoretic analysis. If the acid component and the mucolipoprotein prove to be identical, the procedures developed by Winzler^{19, 20} can be used for the estimation of this material.*

Mucoproteins similar to the acid component have been found in the lung⁷ and in the gastric mucosa,¹⁰ and regenerating epithelium is rich in substances which give the metachromatic reaction with toluidine blue.¹⁵ The origin and physiological significance of the acid component is still unknown, however.

SUMMARY

1. Electrophoretic analysis of human plasma in acetate-chloride buffer at pH 4.0 reveals the presence of an acid protein component with a mobility of -2.7×10^{-5} cm.²/volt/sec.

2. The plasma of patients with gastric cancer or cancer of the lung contains significantly greater amounts of this material than is found in the plasma of normal subjects and patients with gastric ulcer or other non-neoplastic diseases. High values have also been found in three of four cases of lymphatic leukemia and in two cases of Hodgkin's disease.

3. Normal values have been found in six patients who have survived gastrectomy for cancer for more than one year.

* A 0.2 per cent solution of "mucoprotein" prepared by Dr. Winzler from normal plasma has been analyzed electrophoretically in this laboratory at pH 4.0. The ascending boundary showed 72 per cent of a component of mobility -2.7×10^{-5} , (the same as our component A) and 28 per cent of a component of mobility -1.1×10^{-5} . Re-examination of the plasma diagrams indicated that when the boundary was large (2 to 3.6 per cent of the total area) 0.5 to 1 per cent of the slower component was probably also present, although it could not be separated from the salt boundary with any degree of accuracy.

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ELECTROPHORETIC STUDIES ON THE PLASMA PROTEINS OF PATIENTS WITH NEOPLASTIC DISEASE

III. Lymphomas and Leukemia

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THIS study was undertaken because no systematic survey of the electrophoretic patterns of plasma proteins of patients with leukemia or the lymphomas has appeared in the literature. Nitsche and Cohen have recently reported a large series of plasma albumin and globulin concentrations in these diseases, determined by the methanol-precipitation method. They found no significant abnormality in lymphatic leukemia; in myelogenous leukemia, however, the albumin content of the plasma was frequently decreased, and in one-third of the cases studied the globulin content was elevated. In Hodgkin's disease the serum albumin was often low, and the globulin was increased in one-fourth of the patients.

Occasional electrophoretic analyses of the plasma in the lymphomas and leukemia have been reported in the literature,^{5, 6, 11} but no characteristic pattern has been demonstrated for these diseases. In a recent review, Stern and Reiner refer to the unpublished electrophoretic analyses of Stern, Rottino and Suchoff on the plasma of patients with Hodgkin's disease. They suggest that the changes in the plasma proteins of their patients "bear a relation to the clinical state of the patients rather than being specific or characteristic for the disease itself."

The studies contained in this report were

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† This work was done under a fellowship grant from the Jane Coffin Childs Memorial Fund for Medical Research.

These studies were made possible by the co-operation of Dr. L. F. Craver and the staff of the Medical Service of Memorial Hospital. Some of the expenses of this investigation were defrayed by a grant from the James Foundation of New York, Inc.

Received for publication, March 1, 1948.

carried out on the plasma of patients with proved diagnoses of Hodgkin's disease, chronic myelogenous and lymphatic leukemia, acute myelogenous leukemia, and lymphosarcoma. In some instances, plasma was taken after the patient had been treated with a nitrogen mustard, which was usually either methyl-bis (β -chloroethyl) amine hydrochloride (HN_2) or tris (β -chloroethyl) amine hydrochloride (HN_3).⁴ Since these agents are known to destroy lymphoid and hematopoietic tissue and occasionally tumor tissue, it was considered possible that substances resulting from the breakdown of these tissues might be detected in the plasma. Secondly, the nitrogen mustards sometimes produce clinical improvement in these diseases, and the changes in the patient's condition might be reflected in the plasma electrophoretic pattern.

In Table 1 the normal average and range of the electrophoretic components of human plasma obtained in this laboratory are given,⁹ and some of the known factors associated with an increase or decrease in the plasma content of these components are listed. This table indicates the relatively uniform ways in which the plasma electrophoretic pattern is altered by a wide variety of noxious agents, infections, injuries, and pathological states. These changes are discussed in more detail in a recent review by Luetscher.⁷

MATERIALS AND METHODS

In all, thirty-six electrophoretic determinations were made on the plasma of twenty-one patients in various stages of Hodgkin's disease, leukemia, and lymphosarcoma. Fasting blood samples were taken and examined ac-

TABLE I
NORMAL CONCENTRATIONS OF THE ELECTROPHORETIC COMPONENTS OF HUMAN PLASMA (IN GM. PER CENT)
AND THE MOST COMMON CAUSES OF ALTERATIONS IN THE LEVELS OF THESE COMPONENTS*

Total Protein		Albumin		α -Globulins		β -Globulin		Fibrinogen		γ -Globulin	
Normal											
Av.	7.04										
Range	(6.31-7.97)	3.79		0.41 (α_1)	0.62 (α_2)	0.86		0.39		0.74	
		(3.35-4.35)		(0.28-0.62)	(0.53-0.81)	(0.63-1.18)		(0.32-0.59)		(0.49-0.87)	
Nature of change		Elev.	Decr.	Elev.	Decr.	Elev.	Decr.	Elev.	Decr.	Elev.	Decr.
Cause of Change	Not		Earliest change in pattern: seen in protein loss; in defective formation, i.e., malnutrition, liver damage, adrenal insufficiency. (For association with rise in α -globulin, see next column)	Associated with a decrease in albumin in: injury, acute febrile infection, chronic infections and wasting diseases, especially in association with fever	Not seen	Lipemia	Rare	Early or chronic infection; moderate liver damage ^a	Severe liver damage, ^a artefact due to plasma clotting	Infection, particularly in later stages; hypogammaglobulinemia; liver damage	Malnutrition; familial dysproteinemia ^a

* This material is taken from the review of Luetscher⁷ except where other reference is given.

cording to the techniques described in the first paper of this series.⁹ The analyses were made in veronal-citrate buffer of ionic strength 0.10 and pH 8.6. Total plasma proteins were determined by Kjeldahl analysis and corrected for nonprotein nitrogen.

In one patient with lymphosarcoma (H.K.) several samples of a pleural effusion were studied electrophoretically.

RESULTS

The results of the electrophoretic analyses together with the pertinent clinical and laboratory data on each patient at the time that blood was taken for analysis are shown in Table 2.

Hodgkin's Disease. Eight patients with well-established Hodgkin's disease were studied. Six of these patients, in fair general condition, had total plasma proteins within normal limits (with the exception of an elevated value in one, J.B.). Two patients (R.G. and J.W.), in the terminal stage of the disease, were hypoproteinemic.

The serum albumin was moderately to severely lowered in every case, and the α -globulins were increased in seven of the eight cases. The fibrinogen content of the plasma was elevated in every case in which a satisfactory determination was made; the extremely low values obtained on M.L. and J.W. were undoubtedly due to clotting of the plasma. Of the six patients in fair condition, five had a moderately lowered serum albumin (2.7 to 2.3 gm.) and elevated γ -globulin levels. In the two patients in the terminal stage of the disease, on the other hand, the albumin was very low (2.0 and 1.6 gm.) while the γ -globulin was within or below normal limits. One patient (V.M.) fell between the two groups; although her clinical condition was described as fair, she had the low albumin and normal γ -globulin seen in the terminal cases.

One patient (M.L.) is of interest since five electrophoretic patterns were obtained during a ten-month period. The first determination (April 2, 1946) was made when the patient was seriously ill. It showed an abnormal pattern consisting of a low albumin with ele-

vated α -globulins, fibrinogen and γ -globulin. He received a course of nitrogen-mustard therapy, but five days after this treatment (April 8, 1946) his electrophoretic pattern was essentially unaltered. Since clinical improvement was also very slight after this course of treatment, it was repeated. This resulted in a satisfactory clinical remission and the electrophoretic pattern obtained on May 22, 1946, showed a definite return toward normal; the albumin level was elevated to normal, and the α -globulins were decreased. He began to relapse again shortly afterwards, and the plasma examined on June 19, 1946, again showed an abnormal electrophoretic pattern.

The only patient who had no increase in α -globulins (J.B.) had an extraordinarily high γ -globulin value (4.13 gm.) The reason for this was not apparent; it should be noted that he had an eosinophilia of 24 per cent in his peripheral blood, an intense pruritus, and severe skin changes associated with his Hodgkin's disease.

Myelogenous Leukemia. Plasma electrophoretic patterns were obtained on six patients in various stages of myelogenous leukemia. Two of the patients (G.S. and S.K.) were known to have had the disease for at least five years and for three months respectively. They were in good general and nutritional condition; their white blood-cell counts were elevated, extremely immature forms were not seen in the peripheral blood, and their hemoglobin levels were about 11 gm. (75 per cent). Their electrophoretic patterns were essentially normal with the exception of an elevated γ -globulin value in G.S.; this may have been due to the disease, but the presence of an unrelated infection must also be considered.

Two of the patients (A.F. and F.L.) ran very acute courses. A.F. had had chronic myelogenous leukemia for more than one year; it then went precipitously into the acute terminal stage. In F.L. it ran an acute course from the clinical onset of the disease. These patients had a high percentage of myeloblasts in their peripheral blood. They died within six weeks after the electrophoretic patterns

CONCENTRATION OF THE PLASMA PROTEIN COMPONENTS IN PATIENTS WITH LYMPHOMAS AND LEUKEMIA,
WITH THE CLINICAL HISTORY OF EACH PATIENT

Diagnosis	Patient Age Sex	Date	Plasma Proteins						γ	Clinical History
			Total	Alb.	α_1	α_2	β	ϕ		
Hodgkin's Disease	R.C. 34 F	9-11-46	6.81	2.27	0.72	1.02	1.00	0.73	1.07	Onset June, 1946, with cervical adenopathy, controlled by x-rays. Subsequently mediastinal and peripheral adenopathy, and fever up to 102° developed. Hb*-67%, WBC†-9,000 with normal differential. A total of 2 injections of 0.1 mg./Kg. HN ₂ ‡ were given on Sept. 9 and 10, 1946. (In poor condition Oct., 1947.)
Hodgkin's Disease	H.G. 31 M	4-5-47	7.6	2.72	0.85	1.18	1.13	0.81	0.92	Onset Jan., 1946, with axillary adenopathy. Despite repeated x-ray treatments, the disease progressed with weight loss, fever, weakness, and involvement of other lymph nodes and bones. On April 5, 1947, in fair general condition but appeared chronically ill; low-grade fever, generalized adenopathy, and x-ray evidence of extensive osseous lesions were present. Hb-73%, WBC-12,500, normal diff. (In poor condition Jan., 1948.)
Hodgkin's Disease	G.C. 32 F	4-8-47	6.37	2.38	0.66	0.87	0.76	0.73	0.96	Onset 1942, with enlargement of the cervical nodes and mediastinal involvement. The disease was kept under good control by frequent x-ray treatments. In April, 1947, condition fairly good; slight fever and anorexia; infiltration of the right lung base the only evidence of disease. Hb-93%, RBC‡-4,500,000, WBC-13,800, normal diff. (Continues in fair general condition Jan., 1948.)
Hodgkin's Disease	M.L. 30 M	4-2-46	7.42	2.48	0.70	1.41	0.99	0.74	1.10	Onset Nov., 1944, with enlarged cervical nodes; controlled during 1945 by several courses of nitrogen mustard. Began to relapse, in Feb., 1946; on April 2: massive involvement of neck, axillae, and right pectoral region; weak and dyspneic; right hydrothorax. Temperature ranged up to 102°. Hb-50%, RBC-3,500,000, WBC-20,300, normal diff.
		4-8-46	7.42	2.47	0.70	1.38	0.90	0.76	1.21	April 2 to 3, 1946, 0.6 mg./Kg. body weight (33 mg. total) of HN ₂ given. Decrease in fever, and slight regression in the size of diseased tissues by April 8, 1946. Hb-52%, RBC-3,300,000, WBC-7,500, normal diff.
		5-22-46	7.42	3.47	0.66	0.78	1.11	0.34	1.05	Complete clinical remission not obtained; HN ₂ given again during April 29 to May 4, 1946. Nodes decreased in size and Hb rose spontaneously. On May 22, 1946, in clinical remission. Hb-74%, RBC-3,700,000, WBC-5,900, normal diff.
		6-19-46	6.54	2.54	0.75	1.08	0.99	0.29	0.89	June 19, 1946, lymph nodes again enlarging and pleural fluid re-forming; showing early activation of disease. Hb-81%, WBC-29,100.
		2-8-47	7.02	2.38	0.73	1.08	0.91	0.72	1.19	During the next 6 mos. several more courses of nitrogen-mustard therapy given; disease partially controlled. In Dec., 1946, a course of SK 196, a nitrogen-mustard derivative, administered. Two mos. later, Feb. 8, 1947, disease extending. Hb-57%, WBC-10,200, normal diff. (Jan., 1948, fair condition continues but frequent HN ₂ and x-ray therapy required.)

TABLE 2—Continued

Diagnosis	Patient Age Sex	Date	Plasma Proteins					γ	Clinical History
			Total Alb.	α_1	α_2	β	ϕ		
Chronic myelogenous leukemia	A.F. 30 F	12-11-45	6.33	3.11	0.58	0.63	0.76	0.50	Disease diagnosed after splenectomy, Sept., 1944. In good condition until treated to Sept., 1945. WBC then began to rise; thiouracil without effect. On Dec. 11, 1945, complaints of severe weakness, headaches, and severe vomiting; liver moderately enlarged; low-grade fever. Hb-64%, RBC-3,200,000, WBC-441,000 with 14% polys, 12% metamyelocytes, 13% myelocytes, 17% myeloblasts, 4% eosinophilic myelocytes, 3% lymphocytes and 13 nucleated RBC/100 WBC. In terminal stage of chronic myelogenous leukemia.
		12-29-45	6.40	3.28	0.38	0.79	0.76	0.52	
Acute myelogenous leukemia	F.L. 53 M	12-6-45	6.48	3.66	0.41	0.65	0.84	0.31	Disease diagnosed Oct., 1945. In Dec., 1945, general condition fair; low-grade fever, generalized lymphadenopathy, liver and spleen slightly enlarged. Hb-52%, RBC-2,500,000, WBC-233,000 with 15% polys, 1% eosinophils, 7% metamyelocytes, 15% myelocytes, 53% myeloblasts and 8% lymphocytes. (Death, 1 mo. later.)
		9-11-46	6.14	1.95	0.67	0.71	0.94	0.63	
Chronic myelogenous leukemia	E.R. 40 F	9-11-46	6.14	1.95	0.67	0.71	0.94	0.63	Disease diagnosed in 1945, and treated successfully by x-rays. In September, severe oral infection with fever up to 103° developed; in fair condition; enlarged peripheral nodes; spleen greatly enlarged; liver slightly enlarged. The day before blood was taken for electrophoretic analysis, 630 cc. whole blood given. On day blood drawn: Hb-51%, WBC-341,000 with 31% polys, 8% myelocytes and 61% myeloblasts; platelets reduced in number. (Acute, terminal stage of leukemia apparent; death 3 wks. later.)
		7-2-46	7.31	2.18	0.62	0.62	1.16	0.83	
Subacute myelogenous leukemia	E.E. 58 M	7-2-46	7.49	2.24	0.68	0.76	1.08	0.89	Disease began during 1945 with progressive weakness and some bleeding tendencies. In May, 1946, treated with HN ₂ ; fall in WBC and some symptomatic improvement resulted. On July 2, 1946, relapse had ensued; chronically ill; some oral bleeding; moderate peripheral lymphadenopathy; liver moderately enlarged. Temperature ranged up to 101°. Hb-58%, RBC-2,800,000, WBC-52,000 with 20% polys, 3% metamyelocytes, 13% myelocytes, 33% premyelocytes, 28% blasts, and 3% lymphocytes.
		7-6-46	7.49	2.24	0.68	0.76	1.08	0.89	
Chronic lymphatic leukemia	J.Q. 56 M	7-8-46	6.93	2.09	0.61	0.62	1.03	0.85	Between July 2 to 5, 1946, 0.3 mg./Kg. (18 mg. total) HN ₂ and a total of 1000 cc. whole blood given. July 6, 1946, Hb-65%, WBC-11,300.
		7-19-46	6.06	3.05	0.40	0.55	0.85	0.35	
Chronic lymphatic leukemia	J.Q. 56 M	7-19-46	6.06	3.05	0.40	0.55	0.85	0.35	General condition unchanged. On July 8, 1946, Hb-63%, RBC-2,800,000, WBC-8,200 with 25% polys, 10% myelocytes, 20% premyelocytes, 35% myeloblasts, and 10% lymphocytes. (Death, April 4, 1947.)
		7-19-46	6.06	3.05	0.40	0.55	0.85	0.35	
Chronic lymphatic leukemia	J.Q. 56 M	7-19-46	6.06	3.05	0.40	0.55	0.85	0.35	Disease diagnosed early in 1946; enlarged lymph nodes and right pleural effusion. In June, treated for 1 mo. with urthane without effect. July 19, 1946, cervical nodes and spleen greatly enlarged. Hb-75%, RBC-4,200,000, WBC-41,000 with 19% polys, 2% monocytes, 7% blasts, and 72% lymphocytes. Sternal-marrow aspiration smear, 72% lymphocytes. (Death in Dec., 1946.)
		7-19-46	6.06	3.05	0.40	0.55	0.85	0.35	

TABLE 2—Continued

Diagnosis	Patient Age Sex	Date	Plasma Proteins						γ	Clinical History
			Total	Alb.	α_1	α_2	β	δ		
Chronic lymphatic leukemia	M.K. 62 M	7-19-46	6.14	3.17	0.45	0.70	0.85	0.44	0.53	Disease diagnosed Nov., 1945. It progressed slowly. In July, 1946, general condition fair; generalized adenopathy; liver slightly enlarged; spleen greatly enlarged. Hb-66%, RBC-3,200,000, WBC-200,000 with 95% lymphocytes and 5% blast forms. The sternal-marrow aspiration smear showed 88% lymphocytes. 6 gm. urthane given the day before the blood was taken for electrophoretic analysis. (In fair condition in Jan., 1948.)
Chronic lymphatic leukemia	J.B. 55 M	6-17-46	6.25	2.44	0.39	0.58	0.63	0.49	1.71	Weight loss and weakness began in 1943. Several courses of HN ₂ given, which controlled disease somewhat. On June 17, 1946, general condition fair; no fever; no appreciable weight loss; generalized adenopathy; liver and spleen moderately enlarged. Hb-67%, RBC-3,600,000, WBC-120,000 with 97% lymphocytes and 3% polys. The sternal marrow contained 92% lymphocytes.
		7-3-46	6.35	2.62	0.43	0.49	0.65	0.54	1.63	During June 21 to 25, 1946, nitrogen mustard given. On July 3, 1946, no appreciable change in condition; WBC-90,000.
		7-5-46	6.22	2.64	0.39	0.50	0.60	0.54	1.54	On July 4, 1946, 0.1 mg./Kg. body weight (7.0 mg.) of HN ₃ . The following day blood taken for electrophoretic study. General condition fair. Hb-61%, RBC-3,500,000, WBC-84,000 consisting of 99% lymphocytes.
		10-17-46	5.54	2.28	0.57	0.62	0.61	0.45	1.01	General status maintained. Between Oct. 2 to 8, 1946, 0.8 mg./Kg. of body weight (56 mg. total) HN ₂ given because of enlarged lymph nodes. Developed infection of face, with fever up to 102°; treated with blood transfusions and penicillin. On Oct. 17, 1946, infection still progressing and generalized lymphadenopathy and enlargement of liver and spleen persisted. Hb-47%, WBC-122,000 consisting of 100% lymphocytes. (Death in Jan., 1947.)
Lymphosarcoma	M.P. 52 M	12-15-45	6.48	3.53	0.40	0.56	1.05	0.37	0.58	Onset July, 1945, generalized peripheral adenopathy with slow progression. In Dec., 1945, in good condition with generalized peripheral adenopathy, Hb-82%, RBC-4,000,000, WBC-15,000 with 24% polys and 76% lymphocytes. The bone-marrow aspiration smear contained 62% lymphocytes. (Still in good condition, Jan., 1948.)
Reticulum-cell sarcoma	D.B. 65 M	5-7-46	5.60	2.63	0.43	0.74	0.68	0.45	0.68	Onset Jan., 1945, with gradual progression of weakness, generalized adenopathy, enlargement of liver and spleen, and anemia. In May, 1946, appeared in poor condition; afebrile; marked generalized lymphadenopathy; liver and spleen greatly enlarged; pitting edema of the legs. Hb-25%, RBC-1,300,000, WBC-12,000 with 13% polys, 2% monocytes, and 85% lymphocytes. Bone-marrow aspiration smear contained 80% lymphocytes. Given 500 cc. whole blood; 4 days later a sample of blood taken for electrophoretic analysis. (Several clinical remissions with nitrogen-mustard therapy; death in Nov., 1947.)

TABLE 2—Continued

Diagnosis	Patient Age Sex	Date	Plasma Proteins					γ	Clinical History
			Total Alb.	α_1	α_2	β	ϕ		
Lymphosarcoma	A.W. 46 F	2-11-46	5.15	1.59	0.41	0.84	0.78	0.66	0.86
		5-7-46	6.79	2.36	0.55	0.84	1.03	0.51	1.51
		5-23-46	6.05	2.00	0.43	0.64	0.82	0.74	1.42
Lymphosarcoma	H.K. 26 M	12-10-45	7.64	3.38	0.66	1.18	0.91	0.66	0.85
		12-12-45	7.67	3.51	0.69	1.24	1.02	0.38	0.80
		1-9-46	6.07	2.39	0.52	1.12	0.80	0.52	0.70
H.K. chest fl.		1-30-46	7.30	2.57	0.83	1.26	1.16	0.72	0.77
		12-6-45	4.57	2.84	0.24	0.61	0.29	0.14	0.44
		12-21-45	5.48	3.33	0.22	0.43	0.67	0.17	0.66
		12-28-45	4.37	2.63	0.20	0.40	0.48	0.12	0.54

* Hb is the hemoglobin concentration given in per cent of a standard of 15.8 gm. per 100 cc.

† WBC is the white blood cell count per cu. mm.

‡ HN₂ is methyl-bis (β -chloroethyl) amine hydrochloride.

§ RBC is the red blood cell count per cu. mm.

|| HN₃ is tris (β -chloroethyl) amine hydrochloride.

¶ Trace of hyaluronic acid also present.

were obtained. Their patterns, however, were essentially normal except for a slightly lowered albumin in A.F. She had a second electrophoretic analysis made after an intensive course of nitrogen-mustard therapy. The treatment temporarily lowered her leukocyte count, but the pattern remained essentially unaltered.

Two patients were suffering from a subacute form of the disease and had been seriously ill for several months. When the electrophoretic samples were taken, E.R. had a profound anemia, many myeloblasts in her peripheral blood, and a severe oral infection; E.E. had been chronically and severely debilitated for several months. These patients showed considerable alterations in their electrophoretic pattern, with a lowered albumin, slightly elevated α_1 -globulin, and moderately elevated fibrinogen and γ -globulin values. It is of interest that their α_2 -globulin was not increased. Two electrophoretic determinations were made on E.E. shortly after nitrogen-mustard therapy, but no significant change was observed.

Lymphatic Leukemia. Three patients with chronic lymphatic leukemia were studied. Two were in relatively good condition with a moderate anemia and an elevated lymphocyte count. They had a slightly lowered serum albumin, but their electrophoretic patterns were within normal limits otherwise.

Electrophoretic patterns were obtained on four occasions over a period of four months in the third (J.B.), in whom the leukemia ran a chronic, debilitating, and complicated course. He was hypoproteinemic; his serum albumin was consistently lowered and his fibrinogen and α -globulin levels were not elevated even in the presence of an acute infection. His γ -globulin, on the other hand, was consistently increased. Samples obtained on two occasions after a course of nitrogen-mustard therapy showed some increase in the albumin but no significant change in any other component.

Lymphosarcoma. Four of the patients in this series had lymphosarcoma. One patient (M.P.), in whom the disease was extensive but slowly progressive, was in good nutri-

tional condition; his electrophoretic pattern was normal. The second patient (D.B.) had extensive involvement of the liver, lymph nodes and spleen, and a profound anemia. He was hypoproteinemic; his electrophoretic pattern showed a depression in the serum-albumin level, but no appreciable rise in the α -globulins. The third patient (A.W.) had severe pulmonary involvement and progressive cachexia, with a constant fever up to 103° . Her plasma proteins were below normal, and the electrophoretic analysis showed a severe depression in the albumin level with no significant elevation in the α -globulins. The fibrinogen concentration was high. Over a period of three months the γ -globulin rose from 0.86 to 1.46 gm. (the latter figure an average of two determinations sixteen days apart). In the fourth patient (H.K.) the disease ran an acute febrile course. His initial plasma electrophoretic pattern showed a normal albumin, with elevated α -globulin and fibrinogen. A hydrothorax was present, necessitating repeated thoracenteses; the chest fluid contained 4 to 5 gm. per cent of protein. During a seven-week period of observation his serum albumin fell from an average of 3.45 gm. per cent (average of two determinations) to 2.48 gm. per cent (average of two determinations). His α -globulins remained elevated but no appreciable rise in γ -globulin occurred. This patient, incidentally, received nitrogen-mustard therapy sufficient to produce a severe depression of the bone marrow with leukopenia, thrombocytopenia, and anemia. The plasma electrophoretic pattern, taken about the time of the depth of the bone-marrow depression, two weeks after nitrogen-mustard therapy was concluded, showed no significant alteration except for a sharp fall in the serum-albumin concentration. This fall may have been accentuated by the loss of albumin in the thoracentesis fluid.

The chest fluid taken from this patient was examined electrophoretically on three occasions. Its albumin content was slightly below that found in the plasma. The α and β -globulins averaged about one-third of their level in the plasma, while the γ -globulin was about two-thirds of the plasma level.

DISCUSSION

During its course, Hodgkin's disease generally seems to produce an earlier and more severe systemic intoxication than do the other neoplastic diseases of the lymphatic and hematopoietic organs. The electrophoretic patterns seen in moderately advanced Hodgkin's disease are consistent with a chronic infectious or wasting disease. The patients with far-advanced Hodgkin's disease failed to show the rise in γ -globulin found in the less seriously ill individuals.

The presence of chronic and acute myelogenous leukemia did not affect the plasma electrophoretic pattern if the patient was in good general condition, or if the disease ran such an acute course that no gradual deterioration in the patient's condition occurred. If, however, the course was chronic and debilitating, the electrophoretic pattern was altered with a decrease in serum albumin and some elevation in the α_1 - and γ -globulin and fibrinogen levels.

Chronic lymphatic leukemia was not associated, per se, with any significant alteration in the electrophoretic pattern. One patient with severe, progressive, debilitating disease showed a lowered albumin and elevated γ -globulin level, and failed to react to infection with the expected increases in α -globulins and fibrinogen.

No characteristic plasma electrophoretic pattern was found in patients with lymphosarcoma. The seriously debilitated patients all showed decreased albumin levels. In two patients the α -globulins were normal, although one of them showed a rise in γ -globulin. A third patient had elevated α_2 -globulin and fibrinogen levels, but failed to show a rise in γ -globulin.

It should be noted that in a previous paper in this series,¹⁰ it was shown that the plasma of patients with Hodgkin's disease and leukemia may contain an abnormal amount, (100 to 250 mg. per cent) of an acid protein with an iso-electric point below pH 4.0. This substance is apparently included with the α -globulins in electrophoretic analyses at pH 8.6 and does not appear as a separate boundary.

In those cases in which electrophoretic an-

alyses were made during and following nitrogen-mustard therapy, no specific changes in the pattern were found. Gjessing and Chan-utin detected no change in the γ -globulin of dogs lethally intoxicated with nitrogen mustard, and Spurr found no anamnestic response in rabbits receiving sublethal doses. It is not surprising, therefore, that no change was found in the γ -globulin concentration of the plasma after therapeutic doses of nitrogen-mustard. In one patient in whom nitrogen-mustard therapy for Hodgkin's disease produced a clinical remission (M.L.), the albumin rose and the α -globulin fell to normal limits; the γ -globulin level showed no significant change.

SUMMARY AND CONCLUSIONS

A total of thirty-six plasma electrophoretic patterns were obtained on twenty-one patients with proved diagnoses of Hodgkin's disease, chronic myelogenous and lymphatic leukemia, acute myelogenous leukemia, and lymphosarcoma. No electrophoretic pattern was obtained that was in any way characteristic of these diseases, and normal patterns were sometimes found in the presence of well-established myelogenous and lymphatic leukemia and lymphosarcoma.

The usual pattern in well-established, moderately advanced Hodgkin's disease was a decrease in albumin and an increase in α -globulins, fibrinogen, and γ -globulin. In the late stages of the disease the albumin was further depressed and the γ -globulin was at or below the normal level. These changes in the electrophoretic pattern are consistent with the systemic intoxication which occurs in these patients.

In the chronic, debilitated or complicated stages of lymphosarcoma and leukemia there was a fall in the serum albumin. In the patients with chronic lymphatic and myelogenous leukemia the γ -globulin was elevated, whereas in the patients with lymphosarcoma it did not tend to be increased above normal. In this small series, none of the patients with lymphatic leukemia and only one of the four with lymphosarcoma showed the rise in α -globulins that was seen in seven of the eight with Hodgkin's disease.

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CONVERSION OF A CANCER-RESISTANT TO A CANCER-SUSCEPTIBLE STRAIN OF MICE BY CHEMICAL MEANS*

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IN the past, two methods have produced experimental mice that continue to give rise to a large number of spontaneous tumors; both are genetic approaches to the control of biological variability. The first method, used primarily in the development of the A strain,¹⁰ consisted of inbreeding by a brother to sister mating without any regard, initially, to the incidence of spontaneous tumors. The second method, used in the production of the C, C₃H, C₁₂I, CHI, and CBA strains, was based upon hybridization to increase biological variability, and thereafter the selection of various sublines by the application of the well-known progeny test, that is, of continuing the descendants of a pair of mice that conformed to type.

The A strain, started in 1921 (Strong), was originally designed to permit the genetic analysis of susceptibility to the transplantation of various breast tumors that were developing primarily in mice of the D and other stocks. The establishment of the A strain was imperative for this investigation, since there were no inbred strains of mice known to me that were available for quantitative biological research at that time. When the transplantation investigation had been completed, the mice of the A strain were continued for other purposes. In the F₁₃ generation, a female mouse developed a spontaneous breast tumor at fifteen months of age. Her granddaughter also developed a spontaneous tumor at 17.5 months. Within a few generations, it became

apparent that the female mice were developing a very high incidence of breast tumors. An attempt was made, therefore, to continue the stock as a source of spontaneous breast tumors. In the F₂₈ generation, two sisters developed spontaneous breast tumors near the two extreme ends of the distributional curve at 6.5 and at 15.5 months of age. A selection experiment was then set up. In the A₁ subline there was a continuous selection toward the early appearance of breast tumors, whereas in the A₂ subline there was a continuous selection toward resistance to breast tumors by the continuation of the descendants of the most resistant pair of mice in each generation. The A₁ and A₂ sublines are being continued after nineteen years of continuous divergent selection. The incidence of spontaneous tumors in the two sublines is the same and, therefore, justifies the conclusion, as was published some time ago,⁸ that Johanssen's principle, "selection within a pure line is ineffectual," applies to the incidence of spontaneous breast tumors in mice. Mice of the A strain, both males and females, also develop a very high incidence of spontaneous lung tumors.

The second method of hybridization and selection was employed in the production of the C strain together with all its various sublines,^{9, 12} It was found that female F₁ 79 developed multiple primary spontaneous breast tumors. She had been mated to her own brother and subsequently to her own son. A selection experiment related to the origin of spontaneous breast tumors was immediately begun from the descendants of this mouse. Selection toward the early appearance of breast tumors gave rise to the C₃H strain. At the present time these mice probably show the highest degree of susceptibility to spontaneous neoplastic lesions of mammary origin.

* This experiment has been made possible by grants from The Anna Fuller Fund, The Jane Coffin Childs Memorial Fund for Medical Research and The Committee on Growth of the National Research Council acting for The American Cancer Society.

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Received for publication, December 15, 1947.

Selection toward resistance to cancer produced the CBA stock which at one time showed a very low incidence of tumors and the mice showed an average life span of more than 24 months. In fact, these CBA mice still outlive any other mice in my laboratory. The two other sublines $C_{12}I$ and CHI together with their original C parental stock have an intermediate degree of susceptibility to breast tumors. Mice of these five inbred lines show approximately the same sequence of susceptibility to tumors induced by methylcholanthrene that they do for the incidence of spontaneous breast tumors.¹⁴ Classified according to high susceptibility to both spontaneous mammary-gland tumors and induced fibrosarcoma, these strains are C_3H , C, $C_{12}I$, CHI and CBA.

This paper will describe a third method for the production of an inbred strain of mice, the individuals of which give rise to a high incidence of spontaneous tumors.

MATERIALS AND METHODS

The origin of the NH strain has been reported several times.^{11, 13} Briefly stated it was as follows: Following a cross of mice between the CBA and N strains, a descendant in the F_0 generation was outcrossed to a mouse of the JK stock. In the F_4 generation following this second outcross the mice were divided into four groups. Three of these groups were continued by brother-sister matings as controls (the NH). Mice of the fourth group were injected with 1 mg. of methylcholanthrene dissolved in 1 cc. of sesame oil at 60 days of age (the NHO), and their descendants, obtained by brother-sister matings, have continued to be so treated. At the present time the F_{25} generation has been obtained, that is, mice of twenty-one generations of brother-sister matings of the NHO descent have received the subcutaneous injection of methylcholanthrene. In the F_{13} generation of the experimentally injected NHO series, a group of mice were separated off from their parents and, from that point on, continued by brother-sister matings without the further injection of methylcholanthrene (untreated descent of the NHO). In other words, this group received (1) no treatment between

the F_1 — F_3 generations (the NH descent), (2) then they received methylcholanthrene for nine generations (between the F_4 — F_{13}) (the NHO descent), and (3) finally were continued as untreated descent (without any further injection of methylcholanthrene) for twelve generations (between the F_{14} — F_{25} generations).

In this paper it is intended to compare the incidence of *spontaneous* tumors that have occurred (1) in the original control descent of the NH subline from the F_4 generation onward in which there has been no injection of methylcholanthrene, with (2) the untreated descent of the NHO from the F_{13} generation onward derived from the subline which had received methylcholanthrene for nine generations (between the F_4 and F_{13}).

RESULTS

The first 500 mice produced from the F_4 generation and continued as controls by brother-sister matings gave rise to three spontaneous bronchogenic carcinomas, at an average age of 570.3 days. The other 497 died of causes other than cancer. The frequency distribution of death for these 497 mice is given on the solid line of Fig. 1. This is an incidence of 0.60 per cent of spontaneous tumors.

In the untreated descent of the NHO following exposure of nine generations of mice to the subcutaneous injection of methylcholanthrene, there have been produced, to date, 797 mice, which have died. Of these, 528 have developed spontaneous tumors of various histological types, whereas 269 have died of causes other than cancer. This is an incidence of 66.2 per cent of spontaneous tumors. The frequency distribution of the spontaneous tumors in mice of this descent is given on the long dash line of Fig. 1, whereas the frequency distribution of death from causes other than cancer for the same descent is given on the short dash line.

The spontaneous tumors that these untreated descendants of the NHO mice now develop vary considerably. The predominate types are (1) bronchiogenic carcinoma, (2) neoplastic lesions of the stomach and (3) leiomyosarcoma arising presumably in relation to the uterus. The stomach lesions are

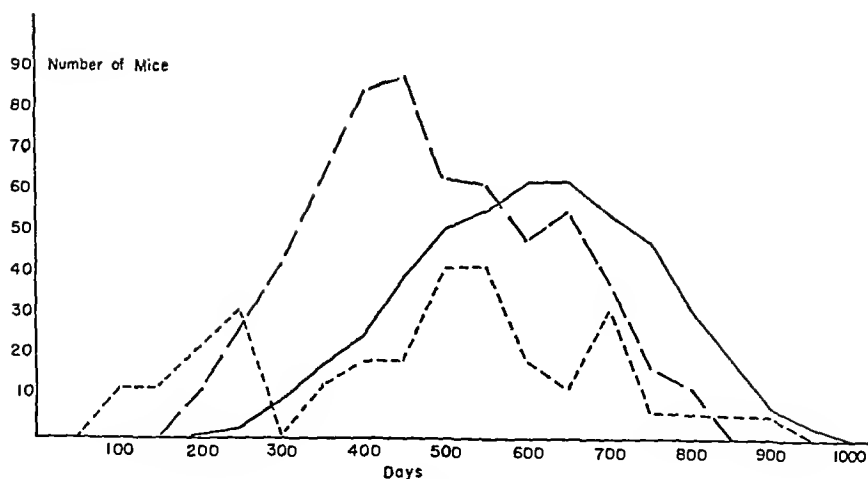


FIG. 1. Distributional curves based upon data obtained on (a) the age at death for the original NH descent (solid line), (b) the age of spontaneous tumors for the untreated descent of the NHO strain following injection of methylcholanthrene into nine successive generations of their ancestors (long dash line) and (c) the age at death from causes other than cancer for the same untreated descent (short dash line). Time in days is expressed on the horizontal, number of mice along the vertical, axis.

of three fundamental types: (a) squamous carcinoma of the forestomach, (b) anaplastic carcinoma arising near the limiting ridge and (c) the proliferative invasive type derived from the mucus-secreting neck cells just anterior to the pylorus. In addition to these five frequently occurring tumors, there have also appeared (4) eight cases of fibrosarcoma that have developed in the right groin spontaneously, (5) epidermoid carcinoma on various parts of the surface of the mice, (6) primary carcinoma of the liver and (7) hepatoma. Two sublines are now being continued (A) in which the incidence of gastric lesions is very high and (B) in which leiomyosarcoma is the dominant type.

The incidence of spontaneous tumors in this untreated descent of the NHO strain is not diminishing in the successive generations, as one would expect if some product of the methylcholanthrene had been introduced into the mice *in utero* or by contact with their nursing mothers, who had been injected with the carcinogen. The incidence of spontaneous tumors is just as high in the F_{20} generation as it had been in the F_{13} .

Another point that should be emphasized is the large number of mice which develop multiple tumors. Many of them develop a

bronchogenic carcinoma as well as a gastric lesion or a leiomyosarcoma of the uterus.

DISCUSSION

The production of strains of experimental mice in which the incidence of spontaneous tumors of mammary-gland origin is very high indicates that something is transmitted from one generation to the next. The fact that Johannsen's principle, "selection within a pure line is ineffectual," applies to the incidence of spontaneous breast tumors was an early indication that this transmission was genetic. The more recent work particularly of Bittner, Lacassagne, Gardner, and others, clearly indicates that superimposed upon this genetic determination there are two other agencies involved, the milk influence and the hormonal. The determination of the exact genetic mechanism involved in the transmission of this mammary-gland-tumor characteristic is, therefore, complex and has not been completely investigated. However, more clear-cut evidence of the genetic determination of lung tumors has been worked out primarily by Heston and Clara J. Lynch. MacDowell has also indicated clearly the genetic influence on leukemia.

The work that has been done in genetics

in relation to cancer susceptibility and resistance clearly indicates that genes are involved in this determination. Since the incidence of spontaneous tumors within a given inbred strain is determined by genes and does not vary from generation to generation, these genes must have been present in the stock at the time of the establishment of inbreeding or have arisen by mutation shortly thereafter.

The recent work of Strong has indicated that the injection of methylcholanthrene into a series of mice for many generations has produced the following biological phenomena: (1) germinal mutations involving hair color, eye color, and distributional patterns of pigmentation, (2) somatic mosaics that are composites of two genotypes, (3) germinal mutations altering susceptibility to the appearance of fibrosarcoma arising at the site of injection of the carcinogen, (4) the production of germinal mutations influencing the occurrence of specific types of tumors that arise not only following the injection of the carcinogen but also subsequently in their untreated descendants, such as proliferative invasive lesions arising in the mucus neck cells of the gastric mucosa and (5) embryological and physiological disturbances that may not be genetic.

The present data on the production of a high cancer line following the exposure of the ancestors to methylcholanthrene for many generations should, therefore, be interpreted in terms of these biological facts. It is highly likely that several mutations have occurred or, in fact, have been induced by the methylcholanthrene that have subsequently increased the incidence of specific types of tumors under spontaneous conditions. Whether the genetic mechanism is the same for the different types of tumors can only be determined by an extensive hybridization and selection experiment. This has not as yet been done. Certainly the separation of this new stock into two sublines, based upon the different incidence of gastric lesions and leiomyosarcoma of the uterus in the two sublines, may indicate that the genetic mechanism for these two types of tumors may be different.

The present data indicate that the biological tendency of mice to give rise to spontaneous tumors can be considerably increased by subjecting the ancestry to methylcholanthrene for many generations. It is suggestive that perhaps the reverse of this phenomena could also be induced by chemical means. The idea is intriguing. However, so far, all changes that have occurred following the injection of methylcholanthrene have been in the direction of increased susceptibility to cancer.

This new strain of mice, the untreated descent of the NHO strain, is now developing spontaneously many types of tumors that appeared for the first time in their ancestors following injection of methylcholanthrene. These ancestral mice had been obtained by a rigid selection toward the suppression of all early-appearing induced tumors such as fibrosarcoma. It is becoming increasingly difficult, therefore, to distinguish between a spontaneously occurring neoplasm and one that develops late in life following the subcutaneous injection of methylcholanthrene. That methylcholanthrene has somehow or other influenced the origin of both series (the induced and subsequent spontaneous) is borne out by the following facts: 1. These new appearing neoplastic lesions, such as the proliferative invasive lesion arising in the mucus neck cells of the gastric mucosa and the leiomyosarcoma of the uterus, have never been obtained in mice of the original control series that have never been injected with methylcholanthrene and have been kept in the same laboratory. 2. When methylcholanthrene has been injected subcutaneously at sixty days of age, these new internal neoplasms occur earlier in life than they do in their subsequent untreated descendants under spontaneous conditions.

SUMMARY

A strain of mice characterized by a very low incidence of spontaneous tumors (0.60 per cent) has been converted into one in which the incidence of spontaneous tumors is very high (66.2 per cent) by subjecting the ancestry of the strain to methylcholanthrene for many generations. In view of the

many germinal changes that methylcholanthrene has induced in mice, this increased incidence of spontaneous tumors of various histological types may have been brought about by mutations in the germ plasma induced by chemical means.

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Current Cancer Literature

This section is intended to provide a comprehensive bibliography of the world journal and book literature. All original articles pertaining to neoplastic disease appearing in American and foreign medical and related scientific journals will be listed and those of more than usual interest, abstracted. In general, editorials and brief conference case presentations will not be included. All reviews and listings of books will appear in this section.

Since the current value of any bibliography depends upon the prompt appearance of all citations and the enduring value upon its ease of use in searching the older literature, a definite starting date, September, 1947, has been chosen: other indexes must be consulted for material appearing prior to this date. Because of the disruption of publishing schedules, it may be some months before certain foreign journals are cited: some South American journals are six or more months behind; many European journals, now resuming publication, are predating their current volumes to maintain a semblance of uninterrupted publication. These will be covered, however, beginning with the appearance of their issues dated September, 1947. No article appearing after December 31, 1947, is included in this issue.

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Gefafer, W. M. [U. S. Pub. Health Serv., Washington, D. C.]: Sickness absenteeism among male and female industrial workers, 1937-46, inclusive. *Pub. Health Rep.* 62: 1538-41, Oct. 24, 1947.—For the years 1937-46 cancer accounted for 0.05% absences.

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Ivy, A. C. [Univ. of Ill., Coll. Med., Chicago, Ill.]: Biology of cancer. *Science* 106: 455-460, Nov. 14, 1947.—This address summarizes past achievements and future possibilities in cancer research. Unequivocal proof now exists that cancer can be cured by removal or destruction if recognized early. The urgent problem today is to prevent, cure, or control advanced cancer.

Study of the hormonal relationships in cancer of the prostate and breast has been productive in the treatment of advanced cancer and demonstrates the importance of basic research, experimental and descriptive. Many fundamental biological questions are unanswered: What is the difference between a benign and a malignant tumor? When tumors invade and metastasize, they have undergone malignant transformation, as demonstrated experimentally in the Shope papilloma and the papilloma induced with tar. However, invasiveness and metastasis are not exclusively the properties of cancer and are not necessarily destructive of the host; e.g., invasion of endometrium by chorionic villi which advances to a certain point, then behaves in a manner analogous to a benign growth. Also, chorionic cells enter the blood stream and pass to the lung but no tumor forms. It is difficult to avoid the view that, fundamentally, benign and malignant tumors are manifestations of the same neoplastic principle, the benign cell representing an arrested or inhibited stage of a potentially

malignant process. Does the cancer cell represent a transformation of a normal cell or a cell abnormal from embryonic life? It is immaterial, except for taxonomic purposes. The important question is: What is the nature of the process induced either into the normal cells or, if preferred, the "embryonal residue" when this becomes cancerous?

The rational approach to the secret of the cure of cancer would seem to be to ascertain either the factors that are responsible for causing unregulated, unlimited, invasive, metastatic, and destructive growth or those responsible for limiting and regulating normal growth. The autonomous nature of a malignant tumor should not be viewed too rigidly. It is difficult to accept the view that any tumor is completely autonomous relative to its rate of growth, although autonomous in its invasive and metastatic properties. A marked similarity exists in the chemical properties (composition, enzyme, and metabolic pattern) of malignant tissues regardless of species or histogenetic source. If the chemistry of malignant tissues or the malignant process is identical for all malignant tumors, one therapy should be applicable to all malignant tumors. The alternate assumption is that various cancers have separate malignant processes, or different stages of the malignant process, and a therapy for each will have to be discovered. Although the malignant process may be the same in all malignant tissues, it may be conditioned or controlled by factors varying with etiology and tissue of origin. Several factors may be concerned in the induction of tumors. Naturally occurring mammary cancers in inbred strains of mice have at least three factors involved: (1) a genetic constitution, or pattern, of inherited susceptibility; (2) the female sex hormone; and (3) the "virus-like" agent transmitted in the milk of the mice.

Accounts of successful inhibition of tumor induction and growth by dietary control appear in the literature but there is a paucity of information in this field in relation to its demonstrated importance. There is no explanation of the natural resistance of certain tissues to the natural development of cancer and to the acceptance of metastases. No one has demonstrated antibodies to cancer tissue in the serum of the host or host immunity to grafts of its own cancer. A great need for a simple test for internal cancer exists. Man is an experimental subject for the study of cancer. Statistics reliably collected and analyzed should provide valuable information regarding the cause and prevention of cancer.—J. A. Chamberlin, M.D.

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- found among the men and 9 among the women. These figures, as well as those from the literature, show a prevalence rate 10 to 15 times that expected in males and twice the expectancy in females. Apparently there are factors at work in the selection of patients presenting themselves for examination in cancer detection centers. One may be the presence of minor complaints and another the occurrence of cancer in the immediate family of the examinees. An incidental, but important, finding was that 36% of men and 51% of women examinees were referred back to their physician because medical or surgical conditions, other than cancer, were discovered.—*Auth. Summ.*
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- Stomach, large intestine, rectum, and liver, in that order, were most commonly affected. Liver cancer deaths fell, probably because of improved methods of diagnosis so that a larger number of liver cancers were correctly recognized as secondary, and the primary foci detected. Code =47 (cancer of larynx, trachea, lung, and mediastinum) manifested a well-marked rise. This was especially reflected in lung cancer, undoubtedly due to the increased use of radiography: 124 cases were recorded in 1936; 209, in 1945. Code =48 (cancer of uterus) revealed little change except in 1945 when a significant rise was recorded: totals were 156 cases in 1936, 201 in 1945. Code =49 (cancer of ovary, vagina, and vulva) was somewhat increased, this being greatest in ovary and vagina: 37 cases in 1936, 70 in 1945. Code =50 (cancer of breast), except for 1943 and 1944, showed little change: 286 cases in 1936, and 269 in 1945; but 316 cases for 1943, and 320 for 1944. Code =51 (cancer of scrotum, prostate, penis, and testicle) showed a steady rise, greatest in prostate cancer: totals were 87 cases in 1936, 146 in 1945; 75 cases of prostate cancer in 1936 but 133 in 1945. Code =52 (cancer of bladder and kidney) showed little change: 70 in 1936, 85 in 1945; males predominated. Code =53 (cancer of ear, face, and other skin) had 106 cases in 1936 against 105 in 1945; but 129 cases were recorded in 1941. It occurred mainly in agricultural workers. Code =54 (cancer of brain, spine, thyroid, and nose) had its highest incidence in females, especially cancer of thyroid. Brain and spine disease was usually secondary. The group as a whole showed a significant rise: 43 cases in 1936, 69 in 1945. Code =55 (cancer of abdomen, arm and leg, axilla, eye, groin, neck, parotid, pelvis, spleen, thorax, throat, and other unspecified organs) revealed 389 cases in 1936, and 283 in 1945. This group undoubtedly included many secondary cancers, perhaps accounting for the greater number recorded in 1936, as compared to 1945 when better diagnostic methods were being employed.
- Whereas the death rate per 100,000 from all cancer was 120.4 in 1936, it was 132.6 in 1945, with the peaks occurring in 1942 (136.9), 1943 (137.2), and 1944 (141.8). Almost 60% of all

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cancer deaths were due to gastrointestinal cancer, particularly in males more than 40 yrs. old. Though there has been a slow, steady rise in cancer deaths in the past 30 yrs. (1911—2427 deaths, 1946—3806 deaths), these statistics are altered somewhat by the increasing number of susceptible persons older than 40 yrs., and by improved diagnostic methods and knowledge. The inexplicable temporary rise in cancer deaths from 1942-1945 was reflected in the tuberculosis death rate during these same years.—*H. D. Diamond, M.D.*

Henschen, Folke [Stockholm, Sweden]: *Ueber Veränderungen im Krankheitspanorama Schwedens während der letzten 50 Jahre.* [Changes in the disease picture in Sweden during the last 50 years.] *Schweiz. med. Wchnschr.* 77: 968-970, Sept. 13, 1947.—Comparative mortality statistics for the period 1900-1946 are given. There has been an increase in breast and prostate carcinoma probably ascribable to the greater number of people in the later decades of life; increase in lung carcinoma beyond that attributable to better diagnosis and increased length of life; a decrease in carcinoma of the upper intestinal tract and an increase in that of the rectum and colon, although carcinoma of the gastrointestinal tract as a whole still accounts for 48% of all carcinoma.—*M. C. J.*

Oughterson, A. W. [New York, N. Y.]: *The control of cancer.* *Ann. Surg.* 126: 478-485, Oct., 1947.

Spies, John W. [Del. State Board of Health, Dover, Del.]: *The cancer program of the State Board of Health.* *Del. State M. J.* 19: 167-168, Sept., 1947.

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ETIOLOGY AND PATHOGENESIS

Ayre, W. B., & Ayre, J. Ernest [Montreal, Quebec]: *Cancer; evolutionary reversion in cell metabolism.* *Am. J. Obst. & Gynec.* 54: 970-981, Dec., 1947.—On the basis of strong suggestive evidence and many facts recently established by various investigators, the authors postulate that the formation of a malignant growth, a cancer, represents an evolutionary reversion in cell metabolism, "an abortive attempt of the regenerating cell to adapt itself to an environment that is deficient in one or more of the elements essential for the formation of the enzyme pattern it requires to become a fully differentiated specialized cell." It is suggested that when the environment of growing cells of the body is compromised, those cells, under stimulus to repair and regenerate, may adapt themselves to that altered environment. The cells continue to grow, but since the environment is inadequate for continued reproduction of fully differentiated cells, the regenerating cells, after many cell generations, revert morphologically and en-

zymatically to cells which have behavior characteristics of the primitive embryonic cell and are malignant. The close similarity between malignant and embryonic tissue, both being rapidly growing tissues and both capable of heterologous transplantation, suggests "that malignant tumors are formed from cells which have resumed certain embryonic characteristics in a disordered growth process." Once formed, malignant tissues, regardless of species origin or of their site of origin within the host, are considered by many authorities so similar biochemically as to constitute a common tissue type.

The enzyme patterns of embryonic and malignant cells have been shown to be similar. Certain components of the vitamin-B complex, particularly riboflavin, niacin, and thiamine, are essential to growing cells for production of their enzyme systems; but embryonic and malignant cells are much less dependent upon these substances than highly differentiated cells. This suggests that differentiated cells, lacking essential components for an enzyme system appropriate for reproduction of their kind, finally reproduce cells whose metabolic requirements are satisfied by the available enzyme pattern. If the deficiency is severe, no growth activity takes place regardless of the stimulus; however, if the deficiency is marginal, the environment may support regeneration of only embryonic cells. Continued regeneration in a marginally deficient cell environment in response to a stimulus is regarded "as the initiating factor in the malignant process in many cancer producing tissues." Some stimulus to cell division is considered essential in the concept of carcinogenesis as presented. The role of chronic irritation, whether it be chemical, mechanical, inflammatory, or radioactive in nature, is generally accepted, and its function as a focalizing factor is suggested by the sites of occurrence of malignant disease. Several clinical studies which suggested the association of marginal deficiency and chronic inflammation in the development of human cancer are cited. One of the authors found in 100 gynecological patients (50 with early uterine cervical cancer and 50 controls) chronic dietary deficiency in 90 per cent of the cancer patients according to the history and determination of thiamine excretion.

The exact role of hormonal agents in carcinogenesis is not established. Their effect is usually marked growth or regression manifested selectively in the tissue concerned. The authors suggest that the action may be alteration of the permeability of the cell membrane to permit or to withhold elements essential for enzymatic systems having to do with growth.

It is suggested that the cell does not acquire new enzyme systems, but that there are only two. One, a basic "primitive" group common to all cells, is responsible for growth and reproduction; the second, superimposed upon the first, is responsible for the specialized tasks of the cell. If the second system is unable to obtain the elements essential to its proper function as in a state of vitamin deficiency and if the cell is stimulated to repeated division, the ca-

capacity for specialized differentiation will be diminished and it will revert to the embryonic form. Such reversion is not inconsistent with Dallo's concept of the irreversibility of evolution as stated in his dictum: "So far as animal structure is concerned, evolution is irreversible, but, regarding adaptation to new stimulating conditions which obtained in the past in another environment, evolution is reversible."

Factors which determine the invasive nature of malignant tumors are suggested. The nucleus of the cell, which contains the growth potential of the cell, is normally kept "starved" of elements essential for growth by the cytoplasmic barrier and the cell membrane. If the cytoplasmic barrier is impaired by chronic subnutrition and the efficiency of the cell membrane altered by hormonal influence, the growth potential of the nucleus is released. Cells with growth potential so released lying next to unaffected tissue find the most nutrition available, grow faster, and hence begin to invade.—*S. A. Wilkins, Jr., M.D.*

Cowdry, E. V. [Wash. Univ. & Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: **Epidermal carcinogenesis.** *J. A. M. A.* 135: 408-412, Oct. 18, 1947.—Coordinated studies of the development of cancer over a 10-yr. period by several groups of workers are summarized. Using methylcholanthrene as carcinogen and the epidermis of a closely inbred strain of mice as tissue, the investigators sought to analyze a biologic equation (Epidermis + Carcinogen Repeatedly Applied → Hyperplastic Precancerous Epidermis → Carcinogen → Squamous Cell Carcinoma) by determining quantitatively the properties of normal untreated epidermis, of epidermis in various stages of hyperplasia, and in the resulting cancer; these are outlined. In precancerous hyperplasia multiple chemical deficiencies predominate as, e.g., in total lipids, calcium, iron and biotin; increases, except for cytochrome oxidase activity, are mild. While the investigators hesitate to attach undue significance to the extent of particular changes, they hold that the fundamentally changed conditions of cell life predispose to mutations having survival value, which may constitute malignant transformation. Conspicuous deficiencies were also found in cancer; but increases were more numerous, the largest being lipid phosphorus, choline, inositol and succinic dehydrogenase activity. Cytochrome oxidase activity was now decreased. While no pattern is discernible, a second and different chemical equilibrium clearly exists and the cell behavior is profoundly modified. Perhaps carcinogens do not generate cancer but set off a sequence of events which, if not broken, may do so. Induced hypersensitivity to the carcinogenic influence of methylcholanthrene and burns has been demonstrated and may be multiple. It is suggested that the decrease in epidermal calcium in cancer "may favor the breaking away and initial invasion of the dermis by malignant cells." The enzyme hyaluronidase has been shown to facilitate the spread of experimental cancer. Antihyaluronidase, along

with correction of the calcium decrease, is hypothesized to prevent spread.—*S. A. Wilkins, Jr., M.D.*

Lachman, Ernest [Univ. Okla. Sch. Med., Oklahoma City, Okla.]: **Common and uncommon pathways in the spread of tumors and infections.** *Surg., Gynec. & Obst.* 85: 767-775, Dec., 1947.

Lartschneider, J. [Linz, Austria]: **Adenomkrebs. Scirrhus, Hornkrebs, Gallertkrebs. Beiträge zur Biologie des Krebsgewebes. [Adenocarcinoma, scirrhus, squamous carcinoma and colloid carcinoma. A contribution to the biology of cancer tissue.]** *Wien. klin. Wchnschr.* 59: 670-672, Oct. 10, 1947.—Microscopic comparative review.

Loeb, Leo [Wash. Univ. Sch. Med., St. Louis, Mo.]: **The causes of cancer.** *Bull. N. Y. Acad. Med.* 23: 564-580, Oct., 1947.—Cancer develops when a combination of growth-stimulating and genetic hereditary factors results in a series of growth processes that gradually gain in intensity. Intermediate steps between normal tissue cells and typical cancer cells are represented by states of increased sensitization as a result of which specific stimuli are no longer needed to produce cancer. The genetic factors act by making the tissues more responsive to growth stimuli. After the cancer stage has been reached, continued stimulation intensifies the process. Concomitantly with the continued stimulation, a growth factor develops within the cell that has the power to propagate autocatalytically, perpetuating the cancer. The cancerous change affects principally those cell characteristics that differentiate tissues and organs within an individual.

Those factors which cause growth processes other than cancer, such as hormonal and regenerative or embryonal growth, may act as partial causes of cancer. There are two classes of growth stimuli: (1) those which stimulate growth without injuring the cells; (2) those which primarily cause tissue injury followed by reparative growth. Cancer-producing hydrocarbons act as direct growth stimulators. However, certain azodyes and substances such as carbon tetrachloride, that produce malignant liver tumors in rats and mice, probably achieve this by liver-cell damage. Certain dietary deficiencies may cause tissue damage that may be followed by cancer.

The only known cancerigenic substances that are normal constituents of the body are the hormones, particularly the sex hormones. These act as growth stimulators inducing proliferation in specific organs. In both clinical and experimental production of cancer by trauma, this must be long continued. Radiations (x-ray, gamma rays, and ultraviolet) cause tissue injury primarily but may also stimulate tissue directly. Metazoan parasitosis may result in the production of substances that stimulate the surrounding tissue to become cancerous. By successive stimulations all of these factors initiate a rhythmic growth process, in which the returns toward the

previously normal state are not quite complete, and which eventuates in cancer. These agents are effective only if the substratum on which they act is able to respond with growth of certain intensity, which in turn is dependent on genetic factors that determine the constitution of the reacting tissue. These genetic factors are probably multiple. A quantitative relationship probably exists between the strength of the stimuli (S), the genetic hereditary factors (H) and the production of cancer (C) — the stronger the genetic factors the less strong need be the stimulating factor ($S \times H = C$). Genetic factors usually act by affecting the degree of response of the organ subjected to stimulation. It is probable that mutations in genes and chromosomes of the germ cells (but not "somatic mutations" strictly speaking) are involved by determining the responsiveness and sensitization of the tissue to growth stimuli (if "somatic mutation" is extended to include steadily increasing cytoplasmic changes, then cancer origin can be attributed to "somatic mutations").

With reservations, it seems that the best explanation of cancer origin is that, as a result of these stimulating factors and the genetic factors, an intracellular growth factor is formed that propagates autocatalytically and is responsible for the irreversible character of cancer. This may act like a virus though of endogenous origin. It is improbable that extraneous viruses are the general immediate cause of cancer.—*M. W. Stearns, M.D.*

Steiner, Paul E. [Univ. Chicago, Ill.]: Human carcinogens. *Ann. West. Med. & Surg.* 1: 269-273, Sept., 1947.

DIAGNOSIS

Anon: Österreichischen Gesellschaft für Erforschung u. Bekämpfung der Krebskrankheit: Zur Frühdiagnose des Karzinoms. Ein Merkblatt für Ärzte. [Early diagnosis of cancer. A suggestion for physicians.] *Krebsarzt* 2: 377-381, Sept., 1947.—Brief diagnostic suggestions for the most common sites for carcinoma.—*M. C. J.*

Benedict, Edward B. [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.]: Endoscopy. *S. Clin. North America* 27: 1191-1214, Oct., 1947.

Dick, Herman J. [Syracuse Univ. Coll. Med., Syracuse, N. Y.]: Staining technic for diagnostic tissue spreads. *Arch. Path.* 44: 396-397, Oct., 1947.—A staining method for aspiration biopsy material that avoids both the loss of cytologic detail coincident to drying and the usually unfamiliar color characteristics of the Papanicolaou stains is presented. Fix spreads for 2 to 20 min. in Schaudinn's solution at room temp. (precise nuclear characteristics are lost if the smear is allowed to dry). Dehydrate in 70% alcohol 5 min. Remove mercury in 70% alcohol to which enough iodine has been added to give a port-wine color—5 min. Rinse in 70% alcohol. Hydrate through 50% alcohol and

water. Stain in Harris' hematoxylin 30 sec. Rinse in tap water. Blue in an alkaline solution 1 to 2 min. Stain with 0.1% eosin 2 min. Dehydrate in graded alcohol, clear in xylene, mount in balsam.—*D. A. S.*

Grosjean, Wendell A. [Winfield, Kan.]: Cancer diagnosis by smears. *J. Kansas M. Soc.* 48: 441-443, Oct., 1947.

Hunter, Warren C., & Richardson, Howard L. [Univ. Oregon M. Sch., Portland, Ore.]: Cytologic recognition of cancer in exfoliated material from various sources. Useful modifications of the Papanicolaou technique. *Surg., Gynec. & Obst.* 85: 275-280, Sept., 1947.—The cytologic recognition of carcinoma in exfoliated material, originally described by Papanicolaou, is reliable in the hands of experienced cytologists and can be applied to a number of organs and systems of the body. A method for paraffin embedding of secretions is described. The fixative of choice is saturated aq. sol. of picric acid. For convenience this may be preceded by 10% formalin in the collecting bottle. Bronchial secretions, material from gastric aspiration, and rectal mucus are placed in the fixative. The fixed material is filtered and the precipitate pressed into the tip of the cone with a glass rod. It is then handled as tissue for embedding. Urine, transudates and exudates are precipitated with picric acid and the product embedded. This method obviates the disadvantage of smear inequality and insures concentration of cells. Vaginal secretions are obtained by inserting a dry speculum into the vagina, bringing it to a horizontal position and milking fluid of the posterior fornix into the posterior blade of the instrument. Smears are made by gloved finger and prepared by the Papanicolaou technique. The remaining fluid is fixed either in picric acid, 70% alcohol or isopropyl alcohol-ether mixture and embedded. The Papanicolaou stain is recommended for fixed sections of all types of secretions.—*J. P. Wozencraft, M.D.*

Leach, John E., & Robbins, Guy F. [Mem. Hosp., New York, N. Y.]: Delay in diagnosis of cancer. *J. A. M. A.* 135: 5-8, Sept. 6, 1947.—A study of the responsibility for the delay in the diagnosis of cancer, which was made in the first three months of 1946, suggests strongly that the patient is making progress in reducing the period of delay, although the physician is not. The principal available means of reducing morbidity and mortality due to cancer are early diagnosis and treatment.—*Auth. Concl.*

Newell, R. R. [San Francisco, Calif.]: California Cancer Commission Studies. Chap. V. Diagnosis and radiation therapy of cancer. *California Med.* 67: 186-191, Sept., 1947.

TREATMENT

Bortz, Donald W., and Haden, Russell L. [Cleveland Clin., Cleveland, O.]: Nitrogen mustard

therapy. Report of 16 cases thus treated. *Cleveland Clin. Quart.* 14: 218-229, Oct., 1947.

Hensel, E. [Wien. städt. Kr.-haus Mödling, Austria]: Die biologische Wirkung der Röntgenstrahlen. [Biological action of x-rays.] *Wien. klin. Wchnschr.* 59: 733-735, Nov. 7, 1947.—A review.

Kenny, Meave [Postgrad. M. Sch. London, England]: Relief of pain in intractable cancer of the pelvis. *Brit. M. J.* 2: 862-863, Nov. 29, 1947.—Seventeen patients with intractable cancer of the uterus, bladder, prostate and vagina were given injections of "proctocaine" (procaine 1.5% w/v, butyl *p*-aminobenzoate 6% w/v, with benzyl alcohol in arachnis oil). 40 to 60 cc. of the warmed solution was injected slowly into the caudal canal. 1 patient had complete relief of pain for the rest of his life (almost 7 mos.) following a single injection. 12 patients had relief of pain from 3 wks. to 4 mos. with 1 to 3 injections. 1 died of thiopentone anesthesia, prior to injection. 2 patients had complete relief for a few days but recurrent pain was unrelieved by further injection. 1 had no relief of pain.—*D. A. S.*

Kérangal, Y., de [Biarritz, France]: Sur le traitement des néoplasies par les thermions métalliques de cuivre. [Treatment of neoplasms by metallic thermions of copper.] *J. méd.*, Paris 67: 173-176, Oct., 1947.

Mody, K. P. [Tata Mem. Hosp.]: The role of x-rays in malignant disease. *Indian J. M. Sc.* 1: 134-140, Sept., 1947.

Ollerenshaw, G. J. W. [Hosa Res. Lab., Sunbury-on-Thames, Eng.]: Some favourable results of H.11 therapy in cancer. *M. World* [London] 67: 43-50, Sept. 5, 1947.—Eleven exemplary case reports.

Plichet, André: Le traitement de certaines affections néoplasiques par les composés azotés de l'ypérite ou gaz moutarde. [Treatment of certain neoplasms by the nitrogen compound, yperite or mustard gas.] *Presse méd.* 55: 587, Sept. 6, 1947.

Wells, John J., & Popp, Walter C. [Mayo Clin., Rochester, Minn.]: The use of pyridoxine hydrochloride in the treatment of radiation sickness: preliminary report. *Proc. Staff Meet., Mayo Clin.* 22: 482-486, Oct. 15, 1947.—Pyridoxine hydrochloride (vitamin B.) intravenously in the treatment of radiation sickness in 200 cases gave a sufficiently high percentage of favorable results to warrant its continuation. The method is safe and relatively inexpensive. At present it seems to be the best method of treatment.—*From Auth. Summ.*

Wolff, Brigitte, & Ellis, Frank [London Hosp., London, Eng.]: Quantitative histological analysis of radiation effects in human carcinomata. *Brit. J. Radiol.* 20: 381-386, Sept., 1947.

RADIOACTIVE ISOTOPES

Bloom, William [Univ. Chicago, Ill.]: Histological changes following radiation exposures. *Radiology* 49: 344-348, Sept., 1947.—External and internal irradiation by x-rays; fast and slow neutrons; gamma rays from radium and the Clinton pile; beta rays from radioactive phosphorus; and internally administered radium, plutonium, sodium, phosphorus, barium, lathanum, strontium, radio zirconium, yttrium and radio cerium was given to mice, rats, rabbits, guinea pigs and chickens—in the range of the LD₅₀, 30-day dose. The pathological changes from the different types of external irradiation were essentially similar; external beta-radiation produced more skin damage and ovarian damage in the mouse. Waves of cell destruction have been observed in the rabbit bone marrow. There is a suggestion of an indirect effect of irradiation, since total body irradiation seemed to produce a greater effect to a given tissue than a similar dose given locally. There was no evidence that small doses of x-rays produced cell stimulation. The belief that young cells or actively dividing cells are unusually susceptible to x-rays was not demonstrated. It appears that some strains of cells, for unknown reasons, are sensitive and others resistant to x-rays; erythroblasts are exceedingly sensitive. The cause of death from irradiation is not known.

Internally administered radioactive materials depend for their effect on the site of localization and the type of radiation emitted, e.g., barium and strontium are localized in bone. In adult mice, in which bone growth has almost ceased, bone and bone-marrow injury occurs. In rats, in which bone continues to grow actively, epiphyseal damage also occurs. Many of the agents localize in the spleen and kidney. The kidney is very resistant to irradiation. Radium alone has produced very serious arteriosclerotic changes in the walls of the great vessels.—*D. A. Karnofsky, M.D.*

Lisco, Hermann; Finkel, Miriam P., & Brues, Austin M. [Univ. of Chicago & Argonne Nat. Lab., Chicago, Ill.]: Carcinogenic properties of radioactive fission products and of plutonium. *Radiology* 49: 361-363, Sept., 1947.—The late effects of various pure beta emitters, strontium⁹⁰, yttrium⁹⁰ and cerium¹⁴⁴ and the alpha emitter, plutonium²³⁹ were studied in mice, rats, and rabbits. Radiostrontium, like radium, was concentrated mostly in bone; and after a latent period of more than 200 days, which increased gradually with decreasing dosage, tumors were produced in the long bones. Radio-yttrium and cerium also produced tumors primarily in the long bones, but plutonium-induced bone tumors occurred mainly in the spine. Plutonium and yttrium (YPO₄) when given subcutaneously or intramuscularly caused graying of the hair, epilation, ulceration of the skin and destruction and atrophy of the muscles, often followed by spontaneous amputation of the injected leg. There were also locally occurring malignant fibrosarcomas in a high percentage

of these animals. Injections of plutonium, cerium and yttrium phosphate also caused liver damage but no hepatomas were seen. In rats fed Y^{90} , there was an increased incidence of adenocarcinoma of the colon.—*J. H. Burchenal, M. D.*

Prosser, C. Ladd [Univ. of Chicago, Ill.]. With contributions by Painter, E. E.; Lisco, Hermann; Brues, Austin M.; Jacobson, Leon O., & Swift, M. N. [Univ. of Chicago, Chicago, Ill.]: **The clinical sequence of physiological effects of ionizing radiation in animals.** *Radiology* 49: 299-313, Sept., 1947.—The different types of ionizing radiation are similar in clinical action. By appropriate selection of doses, dose rate, and experimental animals, similar clinical courses have been seen with single and daily x-radiation, and internal irradiation from deposited α and β emitters. Nearly every organ system is affected by lethal doses of every type of irradiation; but the hematopoietic, gastrointestinal, and reproductive systems are particularly sensitive. The clinical picture varies with dose rate, and duration of exposure. If an animal survives one set of symptoms it is likely to die later of another mechanism. Reactions to irradiation can be divided into immediate, initial, early, acute, subacute, and chronic. With the immediate reaction death occurs during the exposure, with widespread cellular destruction from high irradiation doses. In animals surviving 24-48 hrs. shocklike prostration, diarrhea, urination, lacrimation, hyperemia, and fall in blood pressure are seen. There is a slight leukocytosis during the first 24 hrs. but a severe lymphopenia followed later by granulocytopenia. This primary leukocytosis has not been observed with lethal doses of strontium⁹⁰ or plutonium²³⁹. Early deaths in 4-6 days with evidence of leukopenia, dehydration, hemoconcentration, and gastrointestinal damage are seen in dogs and rats.

Acute reactions occur when doses in the mid-lethal range are delivered at 5-15 r per minute. Deaths usually occur 9-21 days after exposure. Changes consist of an immediate lymphopenia and a granulocytopenia that reaches minimum levels in 2-18 days with very slow recovery in the survivors; anemia reaches minimal levels at 14 days in the rabbit and 25 days in the dog, with recovery in from 1-3 mos., in the survivors. The sedimentation rate increases markedly after the first week. There is delayed clotting time after the first week due to the increase of free heparin in the blood; decrease in platelets and an increase in capillary fragility. Delayed absorption of glucose from the gastrointestinal tract, gastrointestinal hemorrhages, and terminal diarrhea are seen. In the early stages there is increased kidney function, but terminally this decreases. Metabolic abnormalities are manifested in rabbits by weight loss in the first few days, in dogs after the 7th day. This is presumably due to an acceleration of normal catabolism. There is a fall in serum albumins and an increase in the α 3 and α 4 globulins and in the β globulin fibrinogen fractions to double their normal values.

The findings generally associated with sub-

acute reactions to irradiation are aplastic, or a hyperplastic macrocytic type of anemia, liver degeneration, emaciation, and increased fragility of the bones. The chronic type of irradiation deaths in those animals surviving many months are due to ovarian tumors, leukemias, skin carcinomas and, following strontium⁹⁰ or plutonium²³⁹, osteogenic sarcomas. Premature aging is also seen.—*J. H. Burchenal, M. D.*

Turner, Richard B. [Harvard Univ., Cambridge, Mass.]: **Radioactive testosterone.** *Science* 106: 248, Sept. 12, 1947.

ANATOMICAL REGIONS

Chigot, P.-L. [Hôp. Paris]: **Conceptions nouvelles sur le traitement des sarcomes des membres.** [New ideas in treatment of sarcoma of the extremities.] *Rev. gén. clin. et thérap.* 61: 457-459, Oct. 16, 1947.—A review.

Mahoney, J. Francis [Sch. Med. & Grad. Sch. Med., Univ. Pa., & Fitzgerald-Mercy Hosp., Darby, Pa.]: **Irradiation treatment of benign and inflammatory diseases of the head and neck.** *M. Clin. North America* [31]: 1538-1549, Nov., 1947.

ABDOMINAL CAVITY

Brunschwig, Alexander [Mem. Hosp., New York, N. Y.], & **Schlafer, Paul W.** [Univ. Kan. Coll. Med., Kansas City, Kan.]: **Experiences in the surgical treatment of multiple visceral neoplasms.** *Ann. Surg.* 126: 780-787, Nov., 1947.

Hanson, Kenneth B., & Crone, John T. [St. Mary's Hosp., Cincinnati, Ohio]: **Simultaneous occurrence of multiple primary carcinomas within the abdominal cavity.** *Am. J. Surg.* 74: 895-896, Dec. 1947.—Case report of simultaneous papillary cystadenocarcinoma of the ovary, adenocarcinoma of the sigmoid colon, and leiomyoma uteri.

Redon, Henri [Hôp. Paris]: **La chirurgie d'excérèse dans les cancers abdominaux "inopérables."** [Radical surgery in "inoperable" cancer of the abdomen.] *Rev. méd. franç.* 28: 123-124, Sept., 1947.—Review of Brunschwig's work.

Warren, Kenneth W. [Lahey Clin., Boston, Mass.]: **Peritoneal cyst.** *Lahey Clin. Bull.* 5: 185-188, Oct., 1947.

THORACIC CAVITY

Adams, Herbert D. [Lahey Clin., Boston, Mass.]: **Thoracic surgery: its present scope.** *Texas State J. Med.* 43: 430-436, Nov., 1947.

Allison, P. R. [Leeds, Eng.]: **Mediastinal cysts of bronchial origin.** *Thorax* 2: 176-190, Dec., 1947.—Three examples of congenital mediastinal cyst of bronchial origin and situated at the bifurcation of the trachea are described. The 1st

cyst contained over a pint of sterile pus and did not communicate with the bronchus. The 2d cyst contained foul-smelling pus and gas, but apparently did not communicate with the bronchus. Both had given rise to symptoms, and both were successfully removed. In the third, a communication with the left main bronchus was found bronchoscopically and confirmed post-mortem, the patient having died of bronchial carcinoma. This cyst was a casual finding and was apparently symptomless.—*Auth. Summ.*

Barrett, N. R. [St. Thomas's Hosp. & Brompton Hosp., Eng.]: *Advances in thoracic surgery*. Practitioner 159: 298-310, Oct., 1947.

Bradford, Martin L.; Mahon, Hugh W., & Grow, John B. [Fitzsimons Gen. Hosp., Denver, Col.]: *Mediastinal cysts and tumors*. Surg., Gynec. & Obst. 85: 467-491, Oct., 1947.—A classification of mediastinal tumors is presented. The various types of tumors are discussed under separate headings. Emphasis is placed on the importance of thoracotomy for pathological diagnosis, with extirpation of the mass if it is operable. Evidence is presented to show that thoracotomy is a safe, rational procedure with no mortality in properly selected cases. 35 mediastinal cysts and tumors are presented, with 6 additional cases of differential diagnostic conditions.—*Auth. Summ.*

Cesanelli, A., & Tricerri, F.: *Fibrosarcoma intratorácico* [Intrathoracic fibrosarcoma.] *An. de cir.* [Argentina] 12: 264-271, Sept., 1947.—Case report.

Davis, Edgar W., & Salkin, David [Hopemont Sanitarium, Hopemont, W. Va., & W. Va. Univ. Sch. Med., Morgantown, W. Va.]: *Intrathoracic gastric cysts*. J. A. M. A. 135: 218-221, Sept. 27, 1947.—Case report and review of literature.

Gasser, N., & Thurnher, B. [Med. Univ.-klin. Innsbruck, Austria]: *Pancoast-Syndrom bei Brustwandgeschwulst*. [Pancoast syndrome in thoracic wall tumor (sarcoma).] *Wien klin. Wchnschr.* 59: 596-597, Sept. 12, 1947.

Horowitz, Isaac [Vet. Adm., Hartford, Conn.]: *Teratoma of the mediastinum—a case report*. Connecticut State M. J. 11: 978-982, Dec., 1947.

Laehman, Ernest [Univ. Okla. Sch. Med., Oklahoma City, Okla.]: *General principles underlying the x-ray diagnosis of mediastinal tumors*. J. Oklahoma State M. A. 40: 451-453, Nov., 1947.

Smart, Joseph, & Thompson, Vernon C. [London Chest Hosp., London, Eng.]: *Intra-thoracic lipomata*. Thorax 2: 163-168, Sept., 1947.—Case report.

Sommer, Fr., & Demonllin, M. [Hôp. Rég. Sarre, Hombourg]: *Kystes dermoïdes du médiastin inférieur*. [Dermoid cysts of the inferior mediastinum.] *Paris méd.* 37: 473-476, Oct. 4, 1947.—Three case reports.

Strode, J. E. [Honolulu, T. H.]: *Tumors of the chest lying within or adjacent to the mediastinum*. Hawaii M. J. 7: 109-117, Nov.-Dec., 1947.

Sussman, Marey L. [Mt. Sinai Hosp., New York, N. Y.]: *The differentiation of mediastinal tumor and aneurysm by angiocardigraphy*. Am. J. Roentgenol. 58: 584-590, Nov., 1947.—Angiocardigraphic visualization of the heart and great vessels is an important aid in the elucidation of mediastinal masses. Aneurysms ordinarily fill with diodrast along with their vessels of origin. At the same time, other abnormalities in the thoracic vascular structures may be demonstrated. The demonstration fails only when the aneurysm is clotted or when there is a small neck. By contrast, tumors do not impair the integrity of the large vessels except by compression and displacement, or by malignant infiltration which may irregularly constrict or even occlude a large vessel.—*Auth. Summ.*

Thompson, John V. [Indianapolis, Ind.]: *Mediastinal tumors and cysts*. J. Indiana State M. A. 40: 848-853, Sept., 1947.

BREAST

Baker, Everett M. [Univ. Pittsburgh, Pa.]: *Simple adenoma of the breast*. Virginia M. Monthly 74: 505-508, Nov., 1947.—Ten cases of simple adenoma of the breast were found in 103,685 admissions in an obstetrical and gynecological hospital over a period of 20 years, giving an incidence of 1 in 10,000. Simple adenoma of the breast is a benign tumor which may develop at any time during the reproductive period of life. It is usually well encapsulated, freely movable, firm, solid and rarely attached to the skin and surrounding tissues. Differentially, the greatest risk or error may be in the possible presence of malignant disease which may simulate fibroadenoma. Accurate diagnosis is made only by microscopic examination. The treatment is surgical excision.—*Auth. Summ.*

Capron, Pierre [Soc. Méd. & Anat.-Clin. Lille]: *Sur un cas de diabète insipide secondaire à une métastase de cancer du sein*. [A case of diabetes insipidus secondary to metastasis from cancer of the breast.] J. sc. méd. Lille 65: 512-515, Nov. 9, 1947.—One year following mastectomy, with later removal of axillary nodes, metastases occurred to base of the brain. 7800 r to the sella turcica relieved the ensuing diabetes insipidus but had no effect on the metastatic tumor.—*M. C. J.*

Chase, Herbert C. [New York, N. Y.]: *Breast cancer*. Surg., Gynec. & Obst. 85: 712-720, Dec., 1947.

Craig, John M. [Peter Brent Brigham Hosp., Boston, Mass.]: *Leiomyoma of the female breast*. Arch. Path. 44: 314-317, Sept., 1947.—Case report.

Fehr, A. M. [Poliklinik Zürich, Switz.]: *Die Chirurgie des Mammacarcinoms*. [Surgery of car-

- cinoma of the breast.] Schweiz. med. Wchnschr. 77: 949-953, Sept. 6, 1947.
- Hanelin, Henry A.; Williams, Jonathan M.; Wolfson, Sol M., & Wernick, E. Davis [Cook County Hosp., Chicago, Ill.]: Treatment of postoperative swelling of the arm following mastectomy. Preliminary report. Arch. Surg. 55: 723-731, Dec., 1947.
- Hermann, Julian B., & Adair, Frank E. [Mem. Hosp., New York, N. Y.]: Unusual metastatic manifestations of breast carcinoma. Cutaneous hemorrhagic metastasis. Am. J. Surg. 74: 844-849, Dec., 1947.—Report of two cases showing cutaneous metastases with hemorrhagic vesicular characteristics.
- Hyden, Hans: Ergebnisse der operativen Behandlung des Brustdrüsenkrebses im Verein mit der Strahlentherapie. [Results of operative treatment of cancer of the breast in conjunction with x-ray therapy.] Krebsarzt 2: 399-417, Sept., 1947.—A statistical review of breast cancer and of the development of irradiation therefor, including an analysis of 316 (35.3%) evaluable cases out of 894 seen between 1933-1944.—M. C. J.
- Kennedy, A. T., & Jelks, Edward [Jacksonville, Fla.]: Cancer of the breast. A study of one hundred cases at the Duval County Hospital. J. Florida M. A. 34: 343-346, Dec., 1947.
- Mulvany, K. Joyce: Radiotherapy and breast cancer. South African M. J. 21: 897-900, Dec. 13, 1947.
- Nathanson, Ira T. [Harvard M. Sch.; Mass. Gen. & Pondville Hosps., Boston, Mass.]: Hormonal alteration of advanced cancer of the breast. S. Clin. North America 27: 1144-1150, Oct., 1947.
- Oliver, David R., & Sugarbaker, Everett D. [Ellis Fischel State Cancer Hosp., Columbia, Mo.]: The significance of skin recurrences following radical mastectomy. Surg., Gynec. & Obst. 85: 360-367, Sept., 1947.—Local skin recurrence following radical mastectomy almost invariably indicates that the case was primarily inoperable by generally accepted criteria. In 26 cases of local skin recurrences all but 2 had metastatic cancer in the axillary lymph nodes; in 1 of these 2 only 4 nodes were examined. Extensive skin excision was performed: 14 were closed with skin grafts and 12 with skin flaps. 2 of 15 cases with more than 25% and 4 of 11 with less than 25% axillary node involvement are still alive, all with widespread metastases. The average time from operation to time of appearance of skin nodules was 14.4 mos.; from operation to death, 24.3 mos.; from appearance of skin nodules to death, 10.8 [sic] mos. Of those living, the average time from operation to time of writing was 33.5 mos. and from appearance of skin nodules, 22.1 mos.
- The anatomy of mammary lymphatics and the mode of cancer spread are discussed: "the route of metastasis of breast carcinoma to the skin is usually by the superficial fascial lymphatic plexus with vertical growth into the skin. Permeation . . . and embolization in retrograde lymphatic flow are probably the chief modes of metastasis, the latter . . . of primary importance. When the axillary lymph nodes are uninvolved and yet skin metastases appear later, it may be assumed that hemic embolization, direct lymphatic permeation or independent lymphatic embolization without retrograde flow" was responsible. Direct implantation of tumor cells may occur, but is considered negligible. It seems improbable that extensive skin excision would improve the five-year survival rate. Earlier diagnosis and radical surgery and a further narrowing of the criteria of operability are recommended.—S. L. Perzik, M.D.
- Parsons, Willard H. [Vicksburg Hosp. & Clin., Vicksburg, Miss.]: Diagnostic and therapeutic consideration in carcinoma of the female breast. Mississippi Doctor 25: 133-136, Sept., 1947.
- Pendergrass, Eugene P. [Hosp. Univ. Pa., Philadelphia, Pa.]: How to prevent death from breast cancer. J. South Carolina M. A. 43: 257-260, Sept., 1947.
- Roth, Catherine H. [New York, N. Y.]: Testosterone therapy in malignant diseases of female breast and pelvis. M. Woman's J. 54: 17-19, Oct., 1947.
- Rutishauser, E., & Majno, G. [Inst. Path. Genève, Swt.]: L'irradiation préopératoire des carcinomes du sein constatations anatomo-pathologiques. [Preoperative irradiation of carcinoma of the breast. Anatomicopathologic considerations.] Schweiz. med. Wchnschr. 77: 935-949, Sept. 6, 1947.
- Sarasin, Raymond [Genève, Swt.]: Le traitement du cancer du sein du point de vue radiologique. [Treatment of cancer of the breast, from the standpoint of radiology.] Schweiz. med. Wchnschr. 77: 953-958, Sept. 6, 1947.
- Sicard, André: Le problème de la castration dans le traitement du cancer du sein. [Problem of castration in treatment of cancer of the breast.] Bull. méd., Paris 61: 387-389, Sept. 21, 1947.
- Slaughter, Danelly P., & Peterson, Lawrence W. [Univ. Ill. Coll. Med., Chicago, Ill.]: Indications for simple mastectomy. Surg., Gynec. & Obst. 85: 456-460, Oct., 1947.—The operation of simple mastectomy is performed far too frequently for benign breast lesions. The usual operation of this type is inadequate and does not remove completely the breast tissue. Such limited surgery is useful, but not when a diffuse lesion of the breast is being treated, and particularly not when the operation is done for a "precancerous" lesion as prophylaxis against cancer. Such "prophylactic" amputation of a breast should be done only on very well-considered biopsy material, which is interpreted as

showing diffuse duct epithelial changes of atypical hyperplasia of a marked degree. We consider the indications for simple mastectomy to be as follows: 1. Therapeutic, when a diagnosed disease of the breast is being treated. a. Palliative for advanced, inoperable breast cancer with a bulky, ulcerating mass. b. Palliative for cancer in poor risk patients. c. Sarcoma of the breast. d. Chronic suppurative infections of the breast, either nonspecific or tuberculous, which have destroyed much breast tissue. e. The rare case of uncontrollable and severe mastodynia which does not respond to endocrine therapy and which requires opiates for relief. f. The rare case of diffuse fat necrosis throughout the breast, with sinus formation. 2. Prophylactic. a. Multiple or diffuse, and recurrent benign tumors with malignant potentials such as multiple intracystic papillomas, and cystosarcoma phyllodes. b. Precancerous chronic cystic mastitis, showing diffuse duct changes of advanced atypical epithelial hyperplasia.—*Auth. Summ. & Concl.*

Taylor, Grantley W., & Wallace, Richard H. [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.]: Carcinoma of the breast. *S. Clin. North America* 27: 1151-1155, Oct., 1947.

Taylor, Grantley W., & Wallace, Richard H. [Mass. Gen. Hosp., Boston, Mass.]: Carcinoma of the breast. End-results: Massachusetts General Hospital 1933-1935. *New England J. Med.* 237: 475-477, Sept. 25, 1947.—Of 382 cases observed, 328 primary cases are considered. 236 (72%) underwent radical operation; 112 (50.4%) were living without evidence of disease after 5-8 yrs. Of the 40% without axillary node involvement 75.5% were without recurrence; with axillary involvement, 33.3%. Operation was judged to have been ill-advised in 20, for 17 succumbed to recurrence within a year. There were 5 postoperative deaths (2%). Prognosis was poorest in those less than 40 yrs.; best, in those more than 60. The youngest age group had more cases with higher grades of malignancy and with axillary involvement at the time of operation. The cures in those with higher grade malignancy were largely in those of short duration. Malignancy grading by Greenough's criteria proved a consistent basis for prognosis. Prognosis in those with axillary metastases was poor, primarily when axillary node involvement was extensive: 80% of 15 cases with only 1 or 2 nodes were in the cure group. The size of the primary tumor was significant: 89%, with lesions less than 2 cm. in greatest diameter were among the 5-yr. survivors; 18%, with lesions more than 4 cm. Local recurrence was greater when there was axillary involvement and when the primary was larger and of higher grade of malignancy. Biopsy seems not entirely without hazard, since recurrence in the operative field was twice as frequent (15%) in those biopsied. No preoperative x-ray therapy was used and no benefit from prophylactic postoperative irradiation obtained. Improvement in curability may have been due to sharper criteria for operability as

well as improved operative technic. There was no reduction in the delay on the part of patients in reporting for treatment.—*S. A. H'ikins, Jr., M.D.*

Walther, Hans E. [Path. Inst. Univ. Zürich, Switz.]: Untersuchungen über Krebsmetastasen. VII. Mitteilung. Grundsätzliche Betrachtungen zur kombinierten radiochirurgischen Behandlung des Brustkrebses. [Studies of metastases. VII. Basic considerations in the radiological-surgical treatment of breast cancer.] *Schweiz. med. Wchnschr.* 77: 958-960, Sept. 6, 1947.

CARDIOVASCULAR SYSTEM

Ferris, Deward O., & Holmes, Chester L. [Mayo Clin., Rochester, Minn.]: Extensive lymphangioma of scrotum, penis and adjacent areas: report of a case. *J. Urol.* 58: 453-457, Dec., 1947.

Grougerot, H., & Garteaud: Naevus angioma-teux veineux récidivant après opération. [Venous angiomatous nevus recurring after operation.] *Bull. Acad. nat. de méd.* 131: 578-579, Oct. 21, 28, 1947.—About 2 mos. after excision of an angioma of the lower lip in a 54-yr. old woman, it recurred at the same site alike in all ways.—*M. C. J.*

Nissen, Rudolph [New York, N. Y.]: Intrapericardial sarcoma. *J. Internat. Coll. Surgeons* 10: 588-591; 597, Sept.-Oct., 1947.—Case report.

Reals, William J.; Russum, B. Carl, & Walsh, Edmund M. [Creighton Univ. Sch. Med., & Creighton Mem. St. Joseph Hosp., Omaha, Nebr.]: Primary mesothelioma of the pericardium. *Arch. Path.* 44: 380-384, Oct., 1947.—Case report.

Tarlov, I. M. [Jewish Hosp., Brooklyn, N. Y.]: Spinal extradural hemangioblastoma roentgenographically visualized with diodrast at operation and successfully removed. *Radiology* 49: 717-723, Dec., 1947.—Case report.

DIGESTIVE TRACT

Sheinfeld, William [Coney Island Hosp., Brooklyn, N. Y.]: Palliative surgery for advanced gastrointestinal carcinoma in elderly individuals. *New York State J. Med.* 47: 2109-2110, Oct. 1, 1947.

ORAL CAVITY

Bernier, Joseph L. [Dent. Sect., Army Inst. Path., Wash., D. C.]: Odontogenic tumors. *New York State Dent. J.* 13: 560-567, Dec., 1947.

Bernier, Joseph L. [D. C., U. S. Army]: Survey of pathologic specimens from the oral regions seen at the Army Institute of Pathology during World War II. *Mil. Surgeon* 101: 362-

375, Nov., 1947.—Pathologic specimens from the oral regions submitted to the Army Institute of Pathology are tabulated. The discussion is concerned chiefly with the diagnostic criteria used at the Institute as bases for certain diagnoses. It is recognized that these criteria are subject to controversy in certain instances, and no claim is made as to their infallibility. Of particular interest is the high incidence of malignant tumors submitted, especially those which occurred on the lips.—*Auth. Summ.*

Costen, James B. [St. Louis, Mo.]: **Plasmocytoma: report of a case.** *Laryngoscope* 57: 671-675, Oct., 1947.

Fleming, W. E.: **Early carcinoma in a leukoplakial patch.** *Australian J. Dent.* 51: 359-360, Nov., 1947.—Case report.

Negus, V. E. [King's Coll. Hosp., Eng.]: **Some unusual conditions of the throat.** *Practitioner* 159: 436-441, Dec., 1947.—Mixed salivary tumor; mucocele; sarcoma of the tonsil.

Ombredanne, Marcel [Paris]: **Énorme angiome caverneux de la langue chez une fillette de 10 ans. Résultat opératoire.** [Enormous cavernous angioma of the tongue in a 10-year-old girl. Operative result.] *Ann. d'oto-laryng.* 64: 451-454, Aug./Sept., 1947.

Peake, John Day [Mobile, Ala.]: **Cancer of the mouth.** *J. M. A. State Alabama* 17: 183-185, Dec., 1947.

Saltzstein, Harry C., & Johnson, Walter [Detroit, Mich.]: **Combined jaw resection and neck dissection.** *J. Michigan State M. Soc.* 46: 1285-1288, Nov., 1947.

Schulz, Milford D., & Weisberger, David [Mass. Gen. Hosp., Boston, Mass.]: **The sialogram in the diagnosis of swelling about the salivary glands.** *S. Clin. North America* 27: 1156-1161, Oct., 1947.

Seltzer, Albert P. [Philadelphia, Pa.]: **The removal of a parotid tumor by plastic technic.** *M. World* [New York] 65: 349, Nov., 1947.—Case report; adenoma.

ESOPHAGUS

Adams, W. E. [Univ. Chicago, Chicago, Ill.]: **Carcinoma of the esophagus and cardia.** *Nebraska State M. J.* 32: 381-386, Oct., 1947.

Baer, P., & Sicher, K. [Bristol Roy. Hosp., Eng.]: **The association of achalasia of the cardia with oesophageal carcinoma.** *Brit. J. Radiol.* 20: 528-532, Dec., 1947.

Fleming, J. A. C. [London, Eng.]: **Radiotherapy in cancer of the thoracic oesophagus.** *Thorax* 2: 206-215, Dec., 1947.—Fifty-two patients with esophageal cancer treated only by intubation or gastrostomy were autopsied. 41 (79%) showed spread beyond the esophagus including distant metastasis. Half the tumors were less

than 5.1 cm. long but only 11.9% among those of greater length were confined to the esophagus. In 40, symptoms had averaged 3.9 mos. before first medical examination and death occurred 5.2 mos. later. Of 10 additional cases treated by deep x-ray therapy since 1943, 6 are alive, 4 with active carcinoma 6 to 9 mos. after treatment; 2 well 9 mos. and 2 yrs. after treatment. 4 died of cancer 2½ to 6 mos. after treatment. There was temporary relief of dysphagia in 6 cases. Of 800 cases treated by radiotherapy, reported by 10 other authors, only 10 survived 5 yrs., 1 of whom later died of metastases. It is concluded that radiotherapy has cured very few cases of esophageal cancer, nor has any material increase in survival been achieved.—*J. L. Pool, M.D.*

Hiller, Robert I. [Mt. Sinai Hosp. & Milwaukee County Hosp., Milwaukee, Wis.]: **Trans-thoracic esophagostomy. With reports of two cases.** *Wisconsin M. J.* 46: 1011-1014, Oct., 1947.

McPeak, Elsie, & Arons, Walter L. [New England Deaconess Hosp., Boston, Mass.]: **Adenocarcinoma of the esophagus. A report of one case with consideration of the tumor's resemblance to so-called salivary gland tumor.** *Arch. Path.* 44: 385-390, Oct., 1947.

Ogilvie, Heneage [Guy's Hosp., London]: **The early diagnosis of cancer of the esophagus and stomach.** *Brit. M. J.* 2: 405-407, Sept. 13, 1947.

Santy, P. [Lyon], & Mouchet, Alain [Paris]: **Traitement chirurgical du cancer de l'oesophage thoracique.** [Surgical treatment of cancer of the thoracic esophagus.] *J. chir.* 63: 505-526, [Oct.-Nov.] 1947.—A review.

Sweet, Richard H. [Mass. Gen. Hosp., Boston Mass.]: **Carcinoma of the esophagus and the cardiac end of the stomach. Immediate and late results of treatment by resection and primary esophagogastric anastomosis.** *J. A. M. A.* 135: 485-490, Oct. 25, 1947.—Since 1939 at the Massachusetts General Hospital, 141 resections have been performed for carcinoma of the esophagus or cardia of the stomach as follows: 91, transthoracic partial gastrectomy and esophagectomy with primary intrathoracic esophagogastric anastomosis; 50, resection and high anastomosis, 21 below the aortic arch and 29 above. The most important development in pre- and postoperative care has been the prevention of sepsis by the routine use of penicillin and streptomycin. The elimination of inlying Levine tubes, earlier ambulation, more frequent ligation of the superficial femoral veins and earlier oral feeding are considered features of minor importance. Careful attention to the status of the heart has been highly beneficial in reducing cardiac complications. Obvious distant metastases and liver involvement comprised the only contraindication to operation. Persistent fever or intense boring pain and bronchoscopic evidence of invasion or fix-

ation of trachea or bronchi in thoracic esophageal lesions usually indicated inoperability.

The resectability rate in all cases considered suitable for operation was 66.2%. Of the resected cases 66% made an uneventful recovery. The operative mortality was 16.3%. The incidence of complications and mortality was higher in the high-lying lesions. Sepsis is still important in the supra-aortic anastomotic group. Cardiac disorders are the most frequent complication. In 2 cases of leakage of the anastomosis 1 healed spontaneously, 1 terminated fatally. The 3-yr. survival in 30 patients recovering from the operation for lower esophagus or cardia was 39%. The majority of the fatalities from metastases or recurrence occurred during the first 2 yrs. The same tendency is indicated in the midthoracic group. As a palliative procedure resection is superior to any other method yet available. Dysphagia is the most distressing symptom of esophageal carcinoma, and even in those persons dying of recurrent or metastatic disease following resection recurrence at the anastomosis is infrequent. The duration of palliation in 46 gastric cardia patients varied as follows: 9 lived 6 mos. or less; 21 lived 6 mos. to a yr.; 8 lived 12 to 18 mos.; 6 lived 2 yrs.; 1 lived 3 yrs.; and 1 lived 4 yrs.—*M. W. Stearns, M.D.*

Thorek, Philip [Cook County Grad. Sch. Mcd., Univ. Ill.; Am. Hosp., & Alexian Bros. Hosp., Chicago, Ill.]: Surgical treatment for carcinoma of the esophagus. Illinois M. J. 92: 329-337, Dec., 1947.

Woodward, Fletcher D. [Univ. Va. Hosp., Charlottesville, Va.]: Diseases of the esophagus. M. Rec. & Ann. 41: 282-284, Sept., 1947.

STOMACH

Beaumont, G. E. [Middlesex & Brompton Hosps., Eng.]: A case of dyspepsia. (Demonstrated at the bedside by question and answer.) M. World [London] 67: 327-332, Nov. 7, 1947.—Gastric carcinoma.

Bunch, George H. [Columbia, S. C.]: Gastric cancer, a challenge to the medical profession. J. South Carolina M. A. 43: 325-329, Nov., 1947.

Carter, R. A., & Vickers, J. E. [Los Angeles, Calif.]: Certain roentgen manifestations of gastric lesions. California Mcd. 67: 363-367, Dec., 1947.

Colcher, Henry [Goldwater Mem. Hosp., Coll. Phys. & Surg., New York, N. Y.]: Gastroscopy with transparent balloon. Method for the visualization of the "blind areas." Am. J. Mcd. 3: 423-426, Oct., 1947.

Costello, R. C. [East Liverpool City Hosp., East Liverpool, O.]: Carcinoma of the stomach with Krukenberg type of ovarian metastases; report of a case. Ohio State M. J. 43: 941-943, Sept., 1947.

Engel, Gilson Colby [Lankenau Hosp. & Grad. Sch. Mcd., Univ. Pa. Philadelphia, Pa.]: Reducing mortality in gastric carcinoma. J. A. M. A. 135: 687-690, Nov. 15, 1947.

Fairechild, G. Cranston, & Shorter, Alan [Mt. Vernon Hosp., Northwood, Middlesex, Eng.]: Carcinoma of the stomach. Symposium. V. Irradiation of gastric cancer. Brit. J. Radiol. 20: 511-522, Dec., 1947.

Finsterer, Hans [Univ. Vienna, Austria], & Leonardo, Richard A. [Rochester, N. Y.]: Gastric resection. Its history and present status. J. Internat. Coll. Surgeons 10: 639-652, Nov.-Dec., 1947.

Gillespie, H. W. [St. Peter's Hosp. & Botleys Park, Eng.]: Neuroepithelioma of the stomach. Brit. J. Radiol. 20: 433-435, Oct., 1947.—Case report.

Gomez, Jean [Univ., Liège, Belgium]: Sur le schwannome de l'estomac. (A propos de quatre observations). [Schwannoma of the stomach. (With four case reports.)] J. chir. 63: 463-480, [Sept.,] 1947.—A review.

Grout, J. L. A. [Roy. Sheffield Infirmary & Hosp.; & Univ. Sheffield, Eng.]: Carcinoma of the stomach. Symposium. I. A radiologist's point of view. Brit. J. Radiol. 20: 491-501, Dec., 1947.

Jennings, Denys [London Hosp., E.1, Eng.]: Carcinoma of the stomach. Symposium. VI. The statistical approach to gastric cancer. Brit. J. Radiol. 20: 522-527, Dec., 1947.

Kirshen, M. M.; Weinberg, B. J., & Cohen, A. [Mt. Sinai & Michael Rees Hosps., Chicago, Ill.]: Leiomyoma of the stomach. Gastroenterology 9: 466-471, Oct., 1947.—Case report.

Martinson, L. F.; Gillespie, S. R., & Hunter, Arthur [Portland, Ore.]: Transthoracic gastrectomy. Northwest Mcd. 46: 685-689, Sept., 1947.—A program for earlier diagnosis of carcinoma of the stomach is outlined. Total gastrectomy for gastric carcinoma is proposed as a routine, preferably by a transthoracic or combined transthoracic abdominal approach. 2 transthoracic gastrectomies are reported.—*Auth. Summ.*

Matzner, Milton J. [Brooklyn Jewish Hosp., Brooklyn, N. Y.]: Linitis plastica with total gastrectomy. Rev. Gastroenterol. 14: 800-805, Nov., 1947.—Case report.

Meissner, William A. [New Eng. Deaconess Hosp., Boston, Mass.]: Distribution of parietal cells in gastric disease. Arch. Path. 44: 261-268, Sept., 1947.—A series of 200 stomachs surgically resected for gastric carcinoma or for peptic ulcer of the stomach or the duodenum was examined with particular reference to qualitative and quantitative changes in the parietal cells in the different pathologic states. The number of parietal cells diminishes as the pylorus is approached and is somewhat less along the lesser curvature

than in corresponding areas on the walls or greater curvature. The only quantitative change of significance was that in many cases of carcinoma there was a diminution of the number of parietal cells in the body and the fundus of the stomach, whereas in cases of peptic ulcer, especially of duodenal ulcer, such a diminution was less frequent. A reduction of the number of parietal cells was not a constant finding in cancer of the stomach; in many cases of cancer and complete anacidity there was an abundance of parietal cells. No stomach showed complete absence of such cells. As seen in routine stains, there were no qualitative changes in individual parietal cells which could be correlated with ulcer or with cancer.—*Auth. Summ. & Concl.*

Pack, George T.; McNeer, Gordon, & Boolier, Robert J. [Mem. Hosp., New York, N. Y.]: Principles governing total gastrectomy. A report of forty-one cases. *Arch. Surg.* 55: 457-485, Oct., 1947.

Pevaroff, H. H. [Mt. Sinai Hosp., Cleveland, O.]: Benign tumors of the stomach. *Am. J. Surg.* 74: 488-490, Oct., 1947.—Case report of a fibroleiomyoma with malignant change.

Rodgers, H. W. [St. Bartholomew's Hosp.; Radium Inst., & Mt. Vernon Hosp., Eng.]: Carcinoma of the stomach. Symposium. II. Gastroscopy in the diagnosis of gastric cancer. *Brit. J. Radiol.* 20: 502-504, Dec., 1947

St. Johnston, Ronald [Birmingham United Hosp., Ala.]: Gastroscopy in the diagnosis and management of carcinoma of the stomach. *Birmingham M. Rev.* 15: 163-169, Oct., 1947.—Gastroscopy has a fourfold function in carcinoma of the stomach: to confirm clinical and radiological diagnosis, and to show the type of growth; to refute the diagnosis of carcinoma in certain cases where clinical and x-ray examinations suggest it, and thus to save the patient an unnecessary laparotomy; to make the diagnosis of carcinoma when other methods have failed; to assess the operability of a known carcinoma.—*Auth. Summ.*

Segal, Harry L.; Watson, James S., Jr., & Steinhause, Theodore B. [Univ. Rochester, Sch. Med. & Dentistry, Rochester, N. Y.]: Difficulties in the diagnosis and treatment of lesions of the pyloric antrum. *New York State J. Med.* 47: 2292-2298, Nov. 1, 1947.

Shallenberger, Paul L., & Doane, John H. [Guthrie Clin., Sayre, Pa.]: Leiomyosarcoma of the stomach. Case reports. *Guthrie Clin. Bull.* 17: 59-64, Oct., 1947.

Shorter, Alan [Mt. Vernon Hosp., Northwood, Middlesex, Eng.]: The problem of gastric cancer. *Lancet* 2: 842-845, Dec. 6, 1947.

Spencer, F. M., & Collins, E. N. [Cleveland Clin., Cleveland, O.], & Renshaw, R. John F. [Santa Ana, Calif.]: Sarcoma of the stomach. *Cleveland Clin. Quart.* 14: 282-295, Oct., 1947.—Of 1220 malignant neoplasms of the stomach seen from Jan. 1921 through Jan. 1945, 19 were

proved cases of sarcoma: 9 malignant lymphocytoma; 4 reticulum-cell sarcoma; 3 lymphosarcoma of undetermined type; 2 fibrosarcoma; 1 leiomyosarcoma. Age range was 27 to 68 yrs., av. 54.2 yrs.; 15 were in males and 4 in females. Duration of symptoms averaged 10.3 mos. The most common complaint was upper abdominal pain. In 12 the clinical picture resembled peptic ulcer; ulceration of the gastric mucosa was subsequently demonstrated in these but was present in only 2 who did not have ulcer-like symptoms. Weight loss was quite marked. An abdominal mass was palpable in 4 of 16 lymphosarcomas and all of the 3 spindle-cell sarcomas. With the Ewald test meal 4 showed no free hydrochloric acid. All were studied by G.I. series; 6 by gastroscopy. The usual diagnosis was carcinoma or "neoplasm" of the stomach.

The most common findings were hypertrophy of the gastric rugae, large irregular rugae, large irregular ulcerations, diffuse infiltration, and single or multiple polypoid lesions. Delay in emptying time was uncommon. In only 1 was the lesion identified as lymphosarcoma and that was because metastases were found in the cervical lymph nodes. The diagnosis should be suggested by the appearance of polypoid submucous tumors covered by relatively normal mucosa, and the presence of adherent layers of white gelatinous secretions. The recognition of sarcoma from the gross surgical specimen occurred in only 2 of the 15 resected. Considerable difference of opinion exists as to whether the treatment should be surgery, irradiation, or a combination of both. 2 patients living more than 5 yrs. and 2 living more than 3 yrs. were treated by both. The longest survival among 3 patients treated solely by irradiation was 17 mos. The importance of accurate histological diagnosis is stressed, as malignant lymphocytoma shows a more favorable outcome than the reticulum-cell lymphosarcoma. Gastric sarcoma has a more favorable prognosis than does gastric carcinoma.—*M. W. Stearns, M.D.*

State, David; Moore, George, & Wangenstein, Owen H. [Minneapolis, Minn.]: Carcinoma of the stomach. A ten-year survey (1936 to 1945 inclusive) of early and late results of surgical treatment at the University of Minnesota Hospitals. *J. A. M. A.* 135: 262-267, Oct. 4, 1947.—Between 1936 and 1945, 586 patients with gastric carcinoma were seen, and 447 operated upon (operability rate, 76.3%). 307 underwent gastric resection, 31 total and 276 partial, a resectability rate of 52.2%. Operability and resectability rates were 57% and 28% in 1936 as compared with 88% and 80% in 1945. There were 51 postoperative deaths (16.6%). 65% of all resected cases had regional node metastases, extension of carcinoma to other organs, or both. 25 gastrojejunostomies were performed with a mortality rate of 24%. Peritonitis was the main cause of death (28 deaths). The authors stressed that peritonitis was a rare complication after 1940, when all members of the surgical staff began to use the closed method of gastric resection. 47 patients survived 3 yrs.

after surgery. Based on the total number of patients studied, 10.7% survived 3 yrs.; based on the number of gastric resections performed, 29.4% survived 3 yrs. 22 patients were 5-yr. survivors. This represented 6.6% of the total number of patients and 21.5% of the resections performed.—*A. G. James, M.D.*

Steiner, Paul E.; Maimon, Samuel N.; Palmer, Walter L., & Kirsner, Joseph B. [Univ. Chicago, Ill.]: Gastric cancer: comparison of gross and microscopic differences between short term and five-year survivors after gastrectomy. *Proc. Inst. Med. Chicago* 16: 461-463, Nov. 15, 1947.

Stewart, Matthew J. [Univ. Leeds, Eng.]: Carcinoma of the stomach. Symposium. III. Cancer of the stomach: some pathological considerations. *Brit. J. Radiol.* 20: 505-507, Dec., 1947.

Taylor, Hermon [London Hosp. & King's Coll. Hosp., Eng.]: Carcinoma of the stomach. Symposium. IV. The surgical aspect of carcinoma of the stomach. *Brit. J. Radiol.* 20: 507-511, Dec., 1947.

Welch, Claude E. [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.]: Carcinoma of the stomach. *S. Clin. North America* 27: 1100-1105, Oct., 1947.

SMALL INTESTINE

Carnes, Edwin H. [U. S. Marine Hosp., New Orleans, La.]: Reticulum cell sarcoma of the ileum. *Am. J. Surg.* 74: 491-493, Oct., 1947.—Case report.

Clay, A. G. H. [Eng.]: Neurofibrosarcoma of the small intestine associated with von Recklinghausen's disease. *Post Grad. M. J.* 23: 572-574, Dec., 1947.—Case report.

Doub, Howard P. [Henry Ford Hosp., Detroit, Mich.]: Malignant tumors of the small intestine. *Radiology* 49: 441-451, Oct., 1947.—Roentgen examination of the small intestine requires serial studies by fluoroscopy and films taken every half hour until the small bowel is empty. The majority of malignant neoplasms of the small bowel are adenocarcinomas, lymphosarcomas next, and carcinoids most infrequent. These tumors are of two types: constricting—producing obstruction by narrowing the lumen; fungating—producing obstruction by bulk or intussusception. Progressive loss of weight and strength with varying degrees of anemia comprise the usual clinical picture. Pain is common, as is change of bowel habits. A palpable tumor is frequent. X-ray findings consist of central or marginal filling defects, narrowing of the lumen with dilatation of the proximal intestine and obliteration of the mucosal patterns. In this series of 52 malignant tumors of the small intestine 46 were primary: 22 in the duodenum (21 carcinomas, 1 lymphosarcoma); 14 in the jejunum (9 carcinomas, 3 lymphosarcomas, 1 carcinoid, 1

leukemia); 11 were in the ileum (4 carcinomas, 4 lymphosarcomas, 3 carcinoids). 60% of the duodenal tumors were periampullary. Characteristically supra-ampullary tumors are associated with obstructive symptoms, periampullary tumors with jaundice, infra-ampullary tumors with large amounts of vomited bile. Pain is frequent. Tumor was palpable in half. The usual syndrome in jejunal and ileal primaries was obstruction either by tumor or intussusception. There were 5 metastatic tumors: 1 in the duodenum, 2 each in the jejunum and the ileum.—*M. W. Stearns, M. D.*

Foster, D. B. E. [Llandough Hosp., Cardiff, Wales]: Invaginated Meckel's diverticulum containing a tumour, with associated intussusception. *Brit. M. J.* 2: 656, Oct. 25, 1947.—Submucous lipoma.

Harwell, Mallory [Methodist Hosp., Memphis, Tenn.]: Case report. Malignancy of the terminal ileum. *Memphis M. J.* 22: 146-148, Sept., 1947.

Hodges, Fred J.; Rundles, R. Wayne, & Hanelin, Joseph [Univ. Hosp., Univ. Mich., Ann Arbor, and Duke Univ. Sch. Med., Durham, N. C.]: Roentgenologic study of the small intestine. I. Neoplastic and inflammatory diseases. *Radiology* 49: 587-602, Nov., 1947.

Kiefer, Everett D. [Lahey Clin., Boston, Mass.]: Diagnosis of chronic diseases of the small intestine. Symptoms and signs of small intestinal disorders. *Lahey Clin. Bull.* 5: 171-184, Oct., 1947.

Kline, J. R., & Culver, G. J. [Buffalo Gen. Hosp., Buffalo, N. Y.]: Roentgen findings in primary duodenal and paraduodenal malignant lesions. *Am. J. Roentgenol.* 58: 425-438, Oct., 1947.

Lawler, Richard H.; Ragins, Alex B., & Silverstein, J. [Cook County Hosp., Chicago, Ill.]: Submucous lipofibroma of the ileum. *Am. J. Surg.* 74: 820-823, Dec., 1947.—Report of a case—with associated intussusception.

Rabinovitch, J.; Grayzel, D. M.; Swyer, A. J. & Pines, B. [Jewish Hosp. of Brooklyn, Bklyn., N. Y.]: Sarcomas of the small and large intestine. *Surg., Gynec. & Obst.* 85: 333-339, Sept., 1947.—Clinical and pathological findings in 15 cases of sarcoma of the small and large intestine are reviewed. In 7 of these the lesion was a leiomyosarcoma; in 4, lymphosarcoma; in 3, reticulum-cell sarcoma; and in 1, neurofibrosarcoma. The diagnosis of sarcoma of the intestinal tract is difficult, since it simulates other lesions of the intestine.—*D. A. S.*

Sherry, Leroy B. [Pasadena, Calif.]: Lipoma of the ileum causing ileo-ileal intussusception in an adult. *West. J. Surg.* 55: 604-607, Nov., 1947.

COLON

Allen, Arthur W. [Mass. Gen. Hosp. & Harvard M. Sch., Boston, Mass.]: Carcinoma of the large intestine. *S. Clin. North America* 27:

1018-1031, Oct., 1947.—Five case reports with critical analysis of management.

Bacon, Harry E., & Smith, Caleb H. [Temple Univ. M. Sch. & Hosp., Philadelphia, Pa.]: **Hemicolectomy and proctosigmoidectomy with transplantation of transverse colon to anus. A report of eight cases.** *J. Internat. Coll. Surgeons* 10: 661-665, Nov.-Dec., 1947.—An operation, hemicolectomy and proctosigmoidectomy with transplantation of the transverse colon to the anus, has been described. To our knowledge this procedure has not been previously reported. Four illustrative cases are cited, in which the operation served to avoid or to eliminate a colostomy.—*Auth. Summ.*

Brown, Charles H., & Colvert, James R. [Henry Ford Hosp., Detroit, Mich.]: **Analysis of roentgen-ray diagnosis in carcinoma of the cecum and ascending colon.** *Ann. Int. Med.* 27: 936-943, Dec., 1947.

Campbell, Donald D. [McGregor Clin., Hamilton, Ont.]: **Carcinoma of the left colon.** *Canadian M. A. J.* 57: 537-540, Dec., 1947.

Coller, Frederick A., & Berry, Robert L. [Univ. Mich. Hosp., Ann Arbor, Mich.]: **Cancer of the colon.** *J. A. M. A.* 135: 1061-1066, Dec. 20, 1947.—Carcinoma, the most common tumor of the colon, comprises about 7% of all cancer. Surgery at present offers the only hope of cure or palliation. Technical improvement has outstripped improvement of diagnostic skill. The postoperative mortality and morbidity is low, and the end results are good in early treatment. The hope for better results lies in earlier diagnosis. The anatomy and physiology of the colon are discussed. Most colon cancers are not highly malignant histologically. Node involvement is about the same in the right and left half of the colon. Tumor size has no important relation to the number of nodes involved. The sigmoid is most frequently involved, the cecum second. Both sexes are equally affected, most frequently in the 6th and 7th decade.

In a patient over 40 the following symptoms should suggest carcinoma of the colon until it is excluded: abdominal distress severe enough to be definitely identifiable as abnormal; gross rectal bleeding; definite change in bowel habits. An adequate examination should include: digital rectal and sigmoidoscopic examination; barium enema with air contrast studies. The technique of these examinations is discussed in detail. Hemorrhoids should be considered a symptom of rectal or colonic disorders until proved otherwise. Growth and spread are more rapid in younger patients. Anemia and weight loss have no prognostic value. Carcinoma of the right half of the colon has a slightly better prognosis than that of the left. In general, the majority of cancers of the colon causing symptoms for a year or more are incurable. The various operative techniques are discussed. Poor late results are due to advanced tumor spread rather than poor technical methods. Illustrative statistics of incidence and survival are quoted.—*D. A. S.*

Dallos, Arthur [New York, N. Y.]: **Submucous lipoma of transverse colon with intussusception.** *Am. J. Digest. Dis.* 14: 345-348, Nov., 1947.—Case report.

Duran-Jorda, Frederic [Ancoats Hosp., Manchester, Eng.]: **Histopathology of the semisquamous epithelial layer in the colon.** *Rev. Gastroenterol.* 14: 595-602, Sept., 1947.

Hallendorf, Leonard C. [Hershey Hosp., Muscatine, Iowa]: **One stage resection of the sigmoid colon with primary end-to-end anastomosis for malignancy: case report.** *J. Iowa State M. Soc.* 37: 534-538, Dec., 1947.

Hoffman, John M. [Vet. Adm. Hosp., Portland, Ore.]: **Tumor intussusception. A report of two cases.** *Northwest Med.* 46: 950-953, Dec., 1947.—Carcinoma of the cecum.

Jameson, James W., & Mullins, Clinton R. [Concord Hosp., Concord, N. H.]: **Carcinoma of the colon and rectum.** *New England J. Med.* 237: 699-702, Nov. 6, 1947.—Over a 10-yr. period 71 cases of carcinoma of the colon and rectum were seen. Of these, 49 seemed operable; 4 were not treated radically. 45 were operated on for cure, with 1 postoperative death (2% mortality). 28 were treated 3 or more yrs. ago, with 13 still living and well (46% 3-yr. survival rate). Of 18 cases seen 5 or more yrs. ago, 11 were treated for possible cure, and 7 palliatively; 5 survived 5 yrs. or longer. The results leave much to be desired but are not wholly discouraging.—*Auth. Summ.*

Judd, Edward S., Jr. [Mayo Clin., Rochester, Minn.]: **Resection of the cecum and right portion of the colon for malignant tumor.** *J. Kansas M. Soc.* 48: 444-450, Oct., 1947.

Lazarus, Joseph A., & Marks, Morris S. [New York, N. Y.]: **Benign intestinal tumors of vascular origin.** *Surgery* 22: 766-779, Nov., 1947.—Case report and review of literature.

Lowman, Robert M., & Mendillo, Anthony J. [Grace-New Haven Community Hosp., New Haven, Conn.]: **Polypoid cecal masses produced by invaginated appendiceal stumps.** *Connecticut State M. J.* 11: 736-739, Sept., 1947.

Maisel, Bernard, & Foot, N. Chandler [N. Y. Hosp. & Cornell Univ. M. Coll., New York, N. Y.]: **Multiple polyposis of the colon with malignant change involving colon and appendix. Case report.** *Ann. Surg.* 126: 262-269, Sept., 1947.

Mayo, Charles W. [Mayo Clin., Rochester, Minn.]: **The surgical treatment of carcinoma of the right part of the colon.** *Minnesota Med.* 30: 1197-1201, Nov., 1947.

Meltzer, Adolph, & Hackel, Donald B. [Beth Israel Hosp., Boston, Mass.]: **Foreign body perforation of the sigmoid simulating carcinoma.** *Am. J. Surg.* 74: 824-826, Dec., 1947.—Case report.

Pemberton, J. deJ. [Mayo Clin., Rochester, Minn.]: The effect of chemotherapy on surgery of malignant lesions of the colon. *Proc. Staff Mect., Mayo Clin.* 22: 561-565, Dec. 10, 1947.

Ravdin, I. S.; Zintel, Harold A., & Bender, Doris H. [Schs. Med. & Hosp., Univ. Pa., Phila., Pa.]: Adjuvants to surgical therapy in large bowel malignancy. *Ann. Surg.* 126: 439-447, Oct., 1947.

Strelinger, Alexander [Elizabeth, N. J.]: Ileocolic fistula due to cancer of the descending colon. Operative results. *Am. J. Digest. Dis.* 14: 371-373, Nov., 1947.—Case report.

Thorek, Philip [Chicago, Ill.]: Partial colectomy with partial hepatectomy. Carcinoma of the splenic flexure with solitary liver metastasis. *J. Internat. Coll. Surgeons* 10: 606-610, Sept.-Oct., 1947.—Case report.

Windham, Samuel W.; Ellis, John T., & Latiolais, S. G., [Dothan, Ala.]: Combined colostomy and Miller-Abbott tube in the preparation of left sided colon lesions for surgery. *South. Surgeon* 13: 745-751, Oct., 1947.

RECTUM AND ANUS

Abel, A. Lawrence [Eng.]: Carcinoma of the paraoophoron, invading the rectum. *Proc. Roy. Soc. Med.* 40: 834, Nov., 1947.—Case report.

Binkley, George E., & Deddish, Michael R. [Mem. Hosp., New York, N. Y.]: Complications of abdominoperineal resection of rectum for cancer. *New York State J. Med.* 47: 2547-2551, Dec. 1, 1947.

Cole, Clarence H. [Waterbury, Conn.]: Analysis of 34 cases of carcinoma of the rectum and rectosigmoid treated by one stage combined abdominoperineal resection, at the Waterbury Hospital, 1940 to 1946, inclusive. *Connecticut State M. J.* 11: 808-813, Oct., 1947.

Dukes, Cuthbert E. [St. Mark's Hosp., London, Eng.]: An explanation of the difference between a papilloma and an adenoma of the rectum. *Proc. Roy. Soc. Med.* 40: 829-830, Nov., 1947.—There is striking difference in the gross and microscopic appearance of a papilloma and an adenoma. The former is a soft, shaggy tumor and is attached by a broad base extending over a wide area. The latter is a compact, rounded mass of glandular tissue, sessile at first but later attached by a relatively narrow pedicle. The difference in appearance is explained on the basis of different sites of origin. The papilloma is derived from the surface epithelium of the mucosa, the adenoma from the glands. Diagrams are presented, tracing the evolution of each type, according to the author's conception. He believes that carcinoma is more likely to occur in an adenoma than a papilloma. No cases are presented. —D. A. S.

Gabriel, W. B. [St. Mark's Hosp., London, Eng.]: A small high-grade carcinoma of the rectum

with extensive lymphatic spread. *Proc. Roy. Soc. Med.* 40: 833-834, Nov., 1947.—Case report; colloid carcinoma.

Gilechrist, R. K., & David, Vernon C. [Presbyterian Hosp. & Coll. Med. Univ. Ill., Chicago, Ill.]: A consideration of pathological factors influencing five year survival in radical resection of the large bowel and rectum for carcinoma. *Ann. Surg.* 126: 421-438, Oct., 1947.—Two hundred cases of large intestine carcinoma were resected more than 5 yrs. ago when in a stage permitting a reasonable chance of cure. All surgical specimens were cleared, the lymph nodes dissected under transillumination, and the microscopically involved nodes charted by the authors' 1938 method. In all, 114 patients were alive 5 to 10 yrs.: those in whom no lymph-node metastases could be found in the surgical specimens had a 5- to 10-yr. survival rate of 78.5%, showing what can be accomplished by earlier diagnosis; where lymph-node metastases had occurred, 44.8% survived for 5 yrs. There were 112 extraperitoneal rectal carcinomas; 41 intraperitoneal (those below the sacral promontory); 14 sigmoid tumors (those above the sacral promontory); 15 right colon (these include the first 3 in. of transverse colon); 18 left colon (all remaining colon tumors).

Prognosis, recurrence, and mortality rates in the different regions of the colon varied greatly: with node metastases, 37.5% of extraperitoneal rectal and left colon carcinomas; 53.8% of right colon; and 51.4% of intraperitoneal rectal and sigmoid cases were alive and well after 5 yrs.; without node metastases, the rates were 74.4% for extra- and 90% for intraperitoneal. The recurrence rate was 43.5% for all extraperitoneal (23.2% local, 15.9% liver, 4.3% other sites), compared to 18% for all intraperitoneal tumors. If local recurrence be disregarded, prognosis in extraperitoneal rectal carcinoma would be as good as elsewhere in the colon. 18 tumors were in the transverse or descending colon or at the splenic flexure; 8 patients had node metastases (44.4%) of whom 5 died of recurrence within 5 yrs.; 3 lived 5 yrs. (37.5%) in contrast to 80% of those without involved nodes. Apparently resection had been too conservative here. 7 (4.6%) of 153 with carcinomas below the sacral promontory had metastases to lymph nodes 1 to 5 cm. distal to the tumor. This occurs when there is lymphatic blockage and re-emphasizes the need for extensive resection in those having enlarged nodes and large tumors. The lymphatic spread is primarily embolic. The nodes in which the emboli lodge prevent further spread until they are completely overwhelmed by carcinoma; further spread is then through collateral channels: spread from node to node seems uncommon. Thus, involvement of a group of nodes within the field removable by surgery does not mean that a case is hopeless, but indicates the need for the widest possible resection of lymph nodes draining this area.

Resection of fixed tumors and the adherent structures gives a better prognosis than might be expected (40% 5-yr. survival); 20% died

postoperatively. Chemotherapy will undoubtedly lower this figure. 2 of 3 patients who developed rectal carcinoma while pregnant lived more than 5 yrs., suggesting that the gloomy prognosis given pregnant women with neoplasms may not be justified here. Autopsy in 11 of 19 dying in the hospital after resection showed that the ordinary examination usually fails to demonstrate small metastases in the remaining retroperitoneal lymph nodes. Meticulous search of these tissues from the celiac axis to the base of the bladder and prostate was made in 8; 96 to 168 nodes were cleared in each autopsy specimen. In 4, metastases were found in nodes of the retroperitoneal tissues; complete removal of all node metastases would have been obtained in 3 of these had the field of resection been 1.5 cm. wider. In 2, no involved nodes were found in either surgical or postmortem specimens; in 2, none in the postmortem specimen, although present in the surgical. New carcinomas developed in 7 resected cases. Of those who died of recurrence in less than 5 yrs., 2/3 died within 3 yrs., 1/3 between 3 and 5 yrs. 6 who lived 5 yrs. developed recurrences and were dead or dying in less than 7 yrs. Since an appreciable number recur in the 4th and 5th yr. after operation, nothing less than a 5-yr. survival should be considered as a curc. Short-term survivals should not be included in discussions since they lead the general practitioner to false conclusions.

This study indicates the need for the widest possible resection in carcinoma of the colon. Lesions which are partially or completely below the peritoneal reflection have a high incidence of local and liver recurrence, and "pull through" or "sleeve" resections are not much better than a local resection. The Miles operation seems to give the best chance of cure here. In intraperitoneal carcinomas, the David extraperitoneal procedure will allow adequate resection in many; the abdominoperineal resection will give a greater chance of cure in those intraperitoneal lesions below the promontory of the sacrum which are large or have palpably enlarged nodes.—*C. J. Miller, M. D.*

Guzzetta, P. C., Jr., & Cole, W. H. [Univ. Ill. Coll. Med. & Res. and Ed. Hosps., Chicago, Ill.]: Carcinoma of the rectum and anus. *Am. Practitioner* 2: 71-78, Oct., 1947.

Hayden, E. Parker [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.]: Carcinoma of the colon and rectum. *M. Rec. & Ann.* 41: 362-366, Dec., 1947.

Heyd, Charles Gordon [New York, N. Y.]: Surgical procedures for carcinoma of the rectosigmoid and rectum. *New York State J. Med.* 47: 2543-2546, Dec. 1, 1947.

Jackman, Raymond J. [Mayo Clin., Rochester, Minn.]: Submucosal nodules of the rectum: diagnostic significance. *Proc. Staff Meet., Mayo Clin.* 22: 502-504, Oct. 29, 1947.

Kleckner, Martin S. [Allentown, Pa.]: Proctologic surgery of the large bowel. *J. A. M. A.* 135: 545-548, Nov. 1, 1947.—Of 441 cases of

cancer of the large bowel in the author's private practice over a 15-yr. period, 69% were determinable with the gloved finger; 10% of all cases operated upon survived 5 yrs. The majority of patients received salves, soapsuds enemas or suppositories as initial treatment. X-ray studies were made in 17% of 294 rectal carcinomas whereas only a digital examination was necessary for diagnosis. From careful questioning of 304 patients, a change of bowel habits was the earliest symptom obtainable, with bleeding and tenesmus following. When change in bowel habit was the second or third symptom to appear, it was superseded by the aforementioned symptomatology. The time interval between the appearance of the first symptoms and medical consultation was appalling. In 142 [46%] of 304 patients in which this time interval was definitely obtainable, the delay due to the patient's fault was more than 1 yr. This indicates the great need for "jet propulsion" methods in cancer education among the laity. In 70 [37%] of 189 seeking early advice from a physician there was 12 mos. or more delay before surgical aid was urged, a fault of the profession. This poor record was due largely to wrong diagnosis and treatment (almost 23% of the cases). This is indeed a reflection on the status of the physician consulted, and he, alone, can correct this inexcusable calamity. The importance of proctologic, including sigmoidoscopic, examinations prior to all barium study of the colon and the value of taking specimens for biopsy is emphasized.—*C. J. Miller, M. D.*

Marshak, Richard H. [Mt. Sinai Hosp., New York, N. Y.]: Extrinsic lesions affecting the rectosigmoid. *Am. J. Roentgenol.* 58: 439-450, Oct., 1947.

Mathewson, Carleton, Jr., & Richards, Victor [San Francisco, Calif.]: Resection of the rectum and rectosigmoid with primary extraperitoneal end-to-end open anastomosis. *West. J. Surg.* 55: 473-480, Sept., 1947.—Recent studies indicate that lymphatic spread of rectal carcinoma laterally and downwards (Miles) occurs rarely and then only in very low-lying lesions; or in those in which the upward paths of the lymphatics have been blocked by extensive lymphatic infiltration with tumor. To accomplish complete eradication all involved tissues must be excised. This may be prevented by early bloodstream dissemination, so that early rather than radical surgery is paramount. The relative merits of the combined abdominoperineal resection vs. those procedures directed toward preservation of the rectal sphincter is not argued, but a simple and safe method of resection with re-establishment of continuity of the bowel is presented in detail. Primary anastomosis is particularly recommended in those cases demonstrating unresectable metastases. To add a permanent colostomy to an incurable carcinoma is not justifiable if it can be avoided. The primary extraperitoneal anastomosis is a modification of the standardized procedure: an open anastomosis is used with a two-layer closure, the inner consisting of continuous chronic and the outer of interrupted

cotton sutures. All patients are drained from the sacral space through the perincum. The open anastomosis is chosen in preference to a closed technic because: one can determine the exact lowermost level of the lesion and transect the bowel at least 3 cm. below the point of invasion with carcinoma; minute polyps distal to the primary tumor can be recognized; the blood supply of the distal stump at the line of suture is not jeopardized by the clamps necessary to the closed technic; the discrepancy between the size of the lumen of the sigmoid and rectum to be anastomosed is easily and accurately overcome; an anastomosis over clamps is difficult.

19 consecutive resections of the upper rectum and rectosigmoid with primary end-to-end anastomosis and preservation of complete sphincter control were performed with no hospital death. The procedure was carried out palliatively in 6 patients. 2 patients have died since operation; autopsy showed no recurrence at the site of operation. Preliminary transverse colostomy was performed 7 times because of obstruction. Closure of the colostomy was uncomplicated by stricture formation.—*C. J. Miller, M. D.*

Æconomos, Doros [Hôpitaux, Paris]: Cancer double recto-sigmoïdien. [Double cancer of the rectosigmoid.] *Bull. med., Paris* 61: 385-386, Sept. 21, 1947.—Case report.

Pfeiffer, Damon B. [Abington, Pa.]: Treatment of carcinoma of the rectum. *M. World* [N. Y.] 65: 248-251, Sept., 1947.

Ronèche, H., & Bourdais, R.: Considerations sur le caractère familial et héréditaire de la polypose recto-colique essentielle. [The hereditary and familial character of essential rectocolic polyposis.] *Rev. gén. clin. et thérap.* 61: 404-405, Sept. 11, 1947.

Spears, Mary M., & Pfeiffer, Mildred, C. J. [Woman's M. Coll. Pa., Phila., Pa.]: The relationship of anorectal lesions to disease in general. *J. Am. M. Women's A.* 2: 433-436, Oct., 1947.

LIVER AND BILIARY TRACT

Davis, W. D., Jr. [Tulane Univ. Sch. Med. & Ochsner Clin., New Orleans, La.]: Needle biopsy of the liver. *New Orleans M. & S. J.* 100: 159-163, Oct., 1947.

Hager, Henry G., Jr. [Williamsport, Pa.], & Van Camp, Wesley [Pueblo, Colo.]: Primary carcinoma of the gall-bladder in a patient with congenital hemolytic jaundice. *Ann. Int. Med.* 27: 823-827, Nov., 1947.—Case report and review of the literature.

Herrera, Guillermo, & Pardo, Victoriano [Univ. Hosp., Univ. Habana, Cuba]: A new method for biopsy of the liver. *Arch. Path.* 44: 393-395, Oct., 1947.

Kunze, Carl W.; Gall, Edward A.; Schiff, Leon; Molle, William E.; Safdi, Stuart A., & Steinberg, H. Harold [Coll. Med., Univ. Cin-

cinnati, & Cincinnati Gen. Hosp., Ohio]: Needle biopsy of the liver. I. General considerations. *Gastroenterology* 9: 672-681, Dec., 1947.—One hundred ninety-five liver biopsies have been performed on 170 patients without any serious mishap. The lateral (intercostal) approach was used in 180 and the Vim-Silverman needle in 186. 8 cases are not included, since too little time has elapsed to warrant evaluation. In 11 cases the biopsy material was inadequate for diagnosis. Evaluation of diagnostic accuracy in 19 cases could not be determined because of lack of satisfactory proof of the clinical condition. In 85 cases the biopsy diagnosis was in keeping with the clinical and laboratory findings. In 41 cases it was verified by autopsy or operation. In 8 cases the biopsy failed to reveal the presence of the liver lesion or the complete picture of the liver disease subsequently demonstrated at autopsy or operation. In 24 cases the results of liver biopsy corrected incorrect clinical diagnosis. Since deaths have been reported by other observers following either needle or aspiration biopsy of the liver, caution should be exercised in the selection of cases and in the performance of the biopsy and the patient should be carefully observed after the procedure has been done. Final assessment of the safety and value of the procedure must await more widespread experience with it.—*Auth. Summ.*

Layne, John A., & Hildebrand, Eugene [Great Falls Clin., Great Falls, Mont.]: Primary carcinoma of the liver arising in the left lobe and simulating splenomegalia. *Gastroenterology* 9: 603-607, Nov., 1947.

Leiter, H. E. [Mt. Sinai Hosp., New York, N. Y.]: Carcinoma involving the common bile duct. Report of four cases of successful resection. *Surgery* 22: 627-647, Oct., 1947.—A detailed report of 4 cases with a comprehensive survey of the literature.

Slatterly, R. V., & Reals, W. J. [Creighton Univ. Sch. Med., Omaha, Nebr.]: Carcinoma of the extrahepatic bile ducts. *Nebraska State M. J.* 32: 395-396, Oct., 1947.—Case report and review of the literature.

Stout, Arthur Purdy [Columbia Univ. & Presbyterian Hosp., New York, N. Y.]: Tumor Seminar. Carcinoma (hepatoma) of liver. *J. Missouri State M. A.* 44: 676; 678, Sept., 1947

Volwiler, Wade, & Jones, Chester M. [Mass. Gen. Hosp. & Harvard M. Sch., Boston, Mass.]: The diagnostic and therapeutic value of liver biopsies—with particular reference to trocar biopsy. *New England J. Med.* 237: 651-656, Oct. 30, 1947.

PANCREAS

Bartlett, Marshall K. [Mass. Gen. Hosp. & Harvard M. Sch., Boston, Mass.]: The status of pancreaticoduodenal resection. *S. Clin. North America* 27: 1032-1036, Oct., 1947.

- Blain, Alexander W., & Jarrin, Nelson [Alexander Blain Hosp. & Clin., Detroit, Mich.]: Resection of the head of the pancreas for carcinoma. *J. Michigan State M. Soc.* 46: 1175-1180; 1183, Oct., 1947.—Case report and discussion of the literature.
- Dashiell, Grayson F., & Palmer, Walter Lincoln [Frank Billings M. Clin., Univ. Chicago, Ill.]: Co-existence of pancreatic carcinoma and duodenal ulcer: report of three cases. *Gastroenterology* 9: 773-777, Dec., 1947.
- Gordon, Benjamin S., & Olivetti, Renzo G. [Vet. Adm. Hosp., Bronx, N. Y.]: Carcinoma of the islets of Langerhans. Review of the literature and report of two cases. *Gastroenterology* 9: 409-424, Oct., 1947.
- Lopez-Kruger, Rodolfo, & Dockerty, Malcolm B. [Mayo Clin., Rochester, Minn.]: Tumors of the islets of Langerhans. *Surg., Gynec. & Obst.* 85: 495-511, Oct., 1947.
- MacKay, A. R. [Spokane, Wash.]: Carcinoma of the ampulla of Vater. *Northwest Med.* 46: 865-867, Nov., 1947.—Case report.
- Nitshe, George A., Jr., & Suckle, H. M. [Univ. Wis. M. Sch. & State Wis. Gen. Hosp., Madison, Wis.]: Leiomyosarcoma of the ampulla of Vater associated with a tumor of the eighth nerve and neurogenic perforation of the duodenum. Report of a case and review of the literature. *Am. J. Clin. Path.* 17: 827-833, Oct., 1947.
- Putzki, Paul S., & Scully, James H. [George Washington Univ. Sch. Med. & Georgetown Univ. Sch. Med., Wash., D. C.]: Radical pancreaticoduodenectomy for carcinoma of the ampulla of Vater and head of the pancreas. Report of a case. *M. Ann. District of Columbia* 16: 485-491, Sept., 1947.
- Reynolds, John T., & Marlowe, William [Univ. Ill. Coll. Med., & Res. & Ed. Hosps.; St. Luke's Hosp., Chicago, Ill.]: The present status of pancreaticoduodenectomy for carcinoma of the ampulla of Vater and of the head of the pancreas. *J. Internat. Coll. Surgeons* 10: 544-548, Sept.-Oct., 1947.
- Riffenburgh, R. S. [Pasadena, Calif.]: Islet cell adenoma of the pancreas. *Am. Practitioner* 2: 276-278, Dec., 1947.—Case report.
- Schafer, Paul W. [Univ. Kan. Sch. Med., Kansas City, Kan.], & Kozy, John S. [Univ. Chicago Clin., Chicago, Ill.]: Radical pancreaticoduodenectomy with resection of the patent portal vein. An experimental study. *Surgery* 22: 959-964, Dec., 1947.—Removal of carcinomas of the head of the pancreas is often inadequate for cure because of the proximity of the portal vein, which is either involved or passes close to or through involved pancreatic tissue. It seemed to the authors that combining present-day technique of pancreaticoduodenectomy with resection of the portal vein and establishment of a superior mesenteric-vena caval shunt would provide adequate surgical treatment for these lesions. 6 healthy dogs were subjected to ligation of the portal vein and implantation of the distal cut end into the vena cava by use of a portal-vein-covered vitallium tube according to the technique of Blakemore and Lord; the anastomoses remained patent without thrombosis. 3 dogs survived until sacrificed after 94, 128, and 140 days. 22 healthy dogs underwent radical combined operation: resection of the major part of the pancreas, duodenum, and lower fifth of the stomach, an end-to-side gastrojejunostomy, then ligation of the portal vein and anastomosis to the vena cava, and finally a cholecystojejunostomy. The portal caval shunt became obstructed in only 1 dog due to kinking of the mesenteric vein. 19 animals failed to survive the operation or died within 7 days from a variety of causes: anesthesia, shock, peritonitis, aspiration bronchopneumonia, cholangitis with liver abscess, and distemper. Since the remaining 3, that lived 47, 84, and 34 days, all died from stomal ulcerations, it would seem that a more extensive gastrectomy or vagotomy is indicated. 7 of the first 8 animals, anesthetized with intraperitoneal nembutal, died within 24 hrs. after operation without regaining consciousness; apparently, liver function is sufficiently impaired to contraindicate the use of barbiturate anesthesia in this procedure. Ether proved satisfactory. Transfusion of large amounts of whole blood was necessary to replace blood lost into the visceral circulation during portal occlusion and into the inferior systemic circulation during caval occlusion. Thus a radical pancreaticoduodenectomy with portal-vein resection is possible in the dog. —S. A. Wilkins, M.D.

ENDOCRINE ORGANS

- Anderson, D. E., & Conrick, Victor [Univ. Sydney, Australia]: Malignant disease of the thyroid: a review of its gross and microscopic pathology with report of a case. *M. J. Australia* 2: 420-426, Oct. 4, 1947.
- Chiche, Paul: Sur le collapsus tensionnel spontané des surrénales hypertensifs. [Spontaneous hypotension in the course of hypertension due to a suprarenal tumor.] *Paris méd.* 37: 466-469, Sept. 27, 1947.
- Goldner, Martin G. [Vet. Adm. Hosp., Fort Logan, Colo.]: Pheochromocytoma with diabetes. A case report and discussion. *J. Clin. Endocrinol.* 7: 716-723, Oct., 1947.
- Horrax, Gilbert [Lahey Clin.; New England Baptist & New England Deaconess Hosps., Boston, Mass.]: The role of pinealomas in the causation of diabetes insipidus. *Ann. Surg.* 126: 725-739, Nov., 1947.
- Mauriac, Bergouignan, & Léger, H. [Hôp. Saint-André]: Maladie de Cushing. [Cushing's disease.] *J. de méd. de Bordeaux* 124: 448-458, Oct., 1947.—Case report.

Neiman, Ben H. [Chicago, Ill.]: Carcinoma of the thymus. *Proc. Inst. Med. Chicago* 16: 463-464, Nov. 15, 1947.

Peterson, Lowell, J. [Minneapolis Vet. Adm. Hosp., Minn.]: Hyperparathyroidism. *Journal-Lancet* 67: 414-422, Nov., 1947.—Including tumors of parathyroids.

Sevit, Simon, & Sehorstein, J. [Mil. Hosp. Head Injuries, Wheatley, Eng.]: A case of pineal cyst. *Brit. M. J.* 2: 490-491, Sept. 27, 1947.

Thompson, Willard O. [Univ. Ill. Coll. Med., & Henrotin & Grant Hosps., Chicago, Ill.]: Endocrine problems after the age of forty-five. *Geriatrics* 2: 325-333, Nov.-Dec., 1947.—Including relation of hormones to carcinoma of the prostate and breast.

CAROTID BODY

Hadjistamoff, Boyan [Sofia Univ., Sofia, Bulgaria]: Double-timed artery ligation. Early report. *Plastic & Reconstruct. Surg.* 2: 239-442, Sept., 1947.

Lahey, Frank H., & Warren, Kenneth W. [Lahey Clin., Boston, Mass.]: Tumors of the carotid body. *Surg., Gynec. & Obst.* 85: 281-288, Sept., 1947.—The diagnostic features and surgical aspects of 18 cases of carotid body tumor are presented with a discussion of the literature. All the tumors were benign. There was equal sex incidence and almost equal involvement of each side of the neck. Swelling in the neck was usually the only symptom; others were pain, hoarseness and dysphagia. 3 tumors were compressible, thrill and bruit were found in 3 and cranial nerve involvement in 2. Differential diagnosis with branchial cyst, aberrant thyroid tumor and neurofibroma is discussed. Total extirpation requires ligating the carotid vessels in about 1/2 the cases. Therefore the authors urge preliminary graded compression of the carotid artery as a test of adequacy of the cerebral circulation. This has only positive value, as two postligation fatalities withstood preoperative compression for 10 minutes 3 times a day without symptoms. 5 tumors were removed without ligation with 1 death caused by internal carotid thrombosis following dislodgement of an arteriosclerotic plaque. 5 tumors were not excised because total removal required carotid ligation. Only the external carotid was ligated in two cases, with no mortality. In 6 cases in which the common, internal and external carotids were ligated, 2 died and 2 who recovered had temporary hemiplegia. Irradiation caused slight reduction in size in 3 tumors. In view of the slow and relatively symptomless growth of these tumors and the hazards of combined common, internal and external carotid ligation, surgical removal necessitating this procedure is advised only in malignant tumors and only after graded carotid compression without symptoms. Small tumors not surrounding vessels and tumors that interfere with swallowing by bulging the pharyn-

geal wall inward should be removed. All laterally located, discrete, and movable neck tumors should be explored.—*S. L. Perzik, M.D.*

Moritsch, Paul: Ein Fall von Karotisdrüsenuumor. [A case of carotid body tumor.] *Krebsarzt* 2: 489-496, Nov., 1947.

Wyndham, Norman [Sydney]: A carotid body tumor. *M. J. Australia* 2: 548-549, Nov. 1, 1947.

THYROID

Crile, George, Jr. [Cleveland Clin., Cleveland, Ohio]: Papillary carcinoma of the thyroid and lateral cervical region. So-called "lateral aberrant thyroid." *Surg., Gynec. & Obst.* 85: 757-766, Dec., 1947.—Twenty-one cases of papillary carcinoma of the thyroid and lateral cervical region are reported. All patients have been followed from 5 to 21 yrs. or their death; only 3 have died from cancer, 1 with local recurrence in the thyroid, 2 with distant metastasis, 9, 15, and 19 years, respectively, after the original thyroidectomy. 1 patient who has refused all treatment is living and well 27 yrs. after the appearance of lateral cervical nodules and 21 yrs. after these nodules were proved to be papillary tumors of the thyroid. A 5-yr. period is useless in judging the results of treatment of papillary carcinoma of the thyroid. 20 or more yrs. may be required before one can be sure that the patient is cured.

In 16 consecutive cases with papillary tumors of the lateral cervical region, a primary tumor in the thyroid was found on careful examination. The lateral cervical nodules are probably metastases from a tumor of the thyroid rather than primary congenital tumors. Lateral cervical tumors may continue to form until the primary tumor in the thyroid is removed. Following this no more lateral cervical nodules appear. In the few cases in which x-rays have been given, the results have been disappointing. Those of excision of the primary tumor and the lateral cervical and mediastinal metastases have been excellent: 4 patients who had 20 or more lateral cervical and mediastinal nodules are well and free of recurrence for from 6 to 10 yrs. after operation. The lateral cervical nodules rarely invade muscles or blood vessels, hence block dissection of the neck is unnecessary. Since most patients are young women, it is an advantage to operate through a thyroidectomy incision or, in the more extensive cases, through an incision parallel to the sternomastoid. The tumor in the thyroid may be very small and often is not palpable before operation; sometimes it was not found until the posteromedial surface was exposed. The tumor usually is scarred or calcified and may not enlarge appreciably over a period of many years although it continues to give rise to lateral cervical metastases. Regardless of the histology of the tumors and regardless of their apparent hopelessness as suggested by the extent of metastasis, the primary tumor in the thyroid and the lateral cervical and mediastinal metastases should be excised.—*Auth. Summ.*

Graham, J. M., & McWhirter, R. [Edinburgh, Scotland]: Carcinoma of the thyroid. Proc. Roy. Soc. Med. 40: 669-680, Sept., 1947.—After analysis of 144 consecutive cases of cancer of the thyroid, of which 97 were histologically proved, the authors suggest certain criteria for the selection of treatment. The average age was 60 yrs. with a range of 18 to 93; incidence, 3.6 females to 1 male whereas that of simple goiter in this nonendemic area was 9 females to 1 male. Histologically the cases (79 of 97) were divided into adenocarcinoma (23%), papillary adenocarcinoma (16%), and undifferentiated carcinoma (61%). Carcinoma arising in fetal adenoma was included in these 3 groups. Squamous metaplasia was not classified as a specific entity, for it was always found to be associated with one of the other types. Sarcoma was considered to be very rare and the suggestive spindle- and giant-cell types were always found in conjunction with cells of definite epithelial character.

Papillary adenocarcinoma was the most slowly growing and least malignant type with an average history of 3 yrs.' duration before reporting for treatment. These were cystic or solid with late fixation and a preponderance of regional node metastases with rare distant vascular spread. Adenocarcinoma revealed an acinous formation with more frequent vascular invasion and local fixation. The average pre-clinic history was 11 mos. The largest group, undifferentiated carcinoma, was the most malignant and rapidly growing tumor. Local fixation was extensive and frequent. Regional nodes were positive in 25% and distant metastases, in 16%. These frequently became inoperable in 1 to 2 mos. after first seen. Histologically they were characterized by masses or sheets of spheroidal and polygonal cells with little or no stroma, often pleomorphic with giant cells. A brief but pertinent differential diagnosis is presented. Special emphasis is placed on some early clinical signs such as the appearance of a nodular goiter in a patient approaching middle age, and recent increase in size or alteration in outline and consistency of a goiter.

An operable tumor is defined as one that is, at the most, only slightly fixed, with or without nonadherent unilateral lymph nodes. In this group (20% of the total 144 unselected cases), they obtained 73% 5-yr. cures. In the inoperable group where adequate x-ray treatment was given, 29% 5-yr. salvage was obtained. Using regression as a sole criterion in 64 inoperable cases receiving adequate x-ray treatment, they found that 55% (11 cases) of the undifferentiated cancer group was extremely radiosensitive; histologically there was no differentiation between the two groups, but clinically the 9 radioresistant ones had a longer history with either a pre-existing adenoma or a nodular goiter. Since no case treated by surgery alone survived 5 yrs., the 14.5% 5-yr. salvage in this group is considered to be the result of x-ray treatment. Some of these tumors were as sensitive as lymphomas. None of the similarly treated inoperable acinous adenocarcinomas (7) or

papillary adenocarcinomas (3) were radiosensitive. Surgery is recommended for all excisable tumors, even with limited fixation. If on one side only, the lobe should be removed with the isthmus. When the nature of a nodule is uncertain, a lobectomy should be performed. With unilateral vein or node involvement in the presence of a slow-growing tumor, combined radical neck dissection and hemithyroidectomy including the isthmus is suggested. Complete thyroidectomy is rarely indicated, for such extensive involvement usually means that complete excision of the growth is impossible. Partial palliative excision is done only in inoperable radioresistant tumors. Postoperative radiation, even though its added value is questioned in excisable adenocarcinomas or papillary adenocarcinomas, is nevertheless given in all cases; it should always be given in undifferentiated carcinoma. In the inoperable, radiosensitive, undifferentiated carcinoma group, x-ray treatment offers the greatest salvage, even in the face of an acute emergency due to obstructive dyspnea wherein a tracheotomy might otherwise be performed.—*S. L. Perzik, M. D.*

Payne, R. I., Crane, A. R., & Price, J. G. [Norfolk General Hosp., Norfolk, Va. and Pennsylvania Hosp., Philadelphia, Pa.]: Thiouracil and carcinoma of the thyroid. Surgery 22: 496-501, Sept., 1947.—A case of early carcinoma of the thyroid is reported occurring in a diffuse toxic hyperplasia of the thyroid which was treated preoperatively with thiouracil and iodine. The question of the carcinogenic potentialities of thiouracil is raised.—*Auth. Summ.*

Rogers, Walter F., Jr.; Asper, Samuel P., Jr., & Williams, Robert H. [Harvard M. Sch. & Boston City Hosp., Boston, Mass.]: Clinical significance of malignant neoplasms of the thyroid gland. New England J. Med. 237: 569-576, Oct. 16, 1947.—544,918 admissions to 3 large general hospitals on the eastern seaboard were analyzed; included were 3221 (0.59%) with goiters. A pathological diagnosis of malignant neoplasm of the thyroid gland was made in 64 cases (1.99% of all with goiter). Tumors classed as highly malignant occurred in the majority who died of malignant neoplasms of the thyroid gland or had widespread extension. There were few deaths and the results of treatment were fairly satisfactory. Usually in those with tumors of moderate or low malignancy, single nodules, particularly in young people, should be removed as should any nodule showing an increase in size, firmness, or fixation. The authors concluded that not all nodular goiters should be removed because: 1. The incidence of malignant neoplasms of the thyroid was low in clinical and autopsy material. 2. Operations on patients with nontoxic goiter are associated with a significant number of complications and are sometimes fatal. 3. Despite "prophylactic" surgery on benign or clinically unsuspected malignant goiters, lesions may later develop or frequently recur. [Other investigators report the incidence of malignant neoplasms of the thyroid

gland in nontoxic goiter as high as 17%; that the complications following operations on patients with nontoxic nodular goiter can be minimal on a well-organized service; and that the recurrence or later development of malignant lesions would be an infrequent occurrence if the proper cancer-eradicating surgery is employed immediately following "prophylactic" surgery that reveals a malignant lesion of the thyroid.]—A. G. James, M.D.

FEMALE GENITAL TRACT

Curtis, Arthur H. [Moderator]: Panel discussion: symposium on gynecologic bleeding. J. A. M. A. 135: 564-566, Nov. 1, 1947.

Garcia, Manuel, & Schlosser, Joseph V. [Charity Hosp. La. & Tulane Univ. Sch. Med., New Orleans, La.]: Radiotherapy for gynecologic cancer. New Orleans M. & S. J. 100: 141-148, Oct., 1947.

Greene, M. S., & Peckham, B. M. [Northwest Univ. M. Sch., Chicago, Ill.]: Vitamin B complex, menorrhagia, and cancer. A critical review. Am. J. Obst. & Gynec. 54: 611-617, Oct., 1947.

Isbell, N. Paul; Jewett, John F.; Allan, Malcolm S., & Hertig, Arthur T. [Free Hosp. Women, Brookline, & Harvard M. Sch., Boston, Mass.]: A correlation between vaginal smear and tissue diagnosis in 1045 operated gynecologic cases. Am. J. Obst. & Gynec. 54: 576-583, Oct., 1947.—A study has been made of 1045 vaginal smears and the corresponding uterine, cervical and/or vaginal tissue sections. In 1000 of these cases 60 malignancies of the uterus, cervix or vagina were encountered. 41 cases of definite or questionable carcinoma-in-situ were discussed separately. In 40 cases of carcinoma of the cervix, 39 were found to have positive smears and 1 did not, an error of 2.5%. In 18 malignancies of the uterus, 15 smears were positive and 3 were negative, an error of 16.6%. 2 carcinomas of the vagina were encountered and both had positive smears with no error. The total error of positive cases called negative is 6.66%. In the remaining 940 cases with negative tissue sections there were 11 false positive vaginal smears; an error of 1.7%. The total combined error of false positive and false negative smears is thus 1.5%. 4 incidental malignancies were encountered including 1 each from the bladder, urethra, vulva and fallopian tube. 8 positive and 5 negative smears were encountered in 13 carcinomas-in-situ of the cervix. Only 1 positive smear was found in 7 carcinomas-in-situ of the endometrium. 4 positive smears were encountered in 13 questionable carcinomas-in-situ of the cervix. No positive smear was found in 8 questionable carcinomas-in-situ of the endometrium.—Auth. Summ.

Newman, Grace T. [Montclair, N. J.]: The vaginal smear as an aid in the diagnosis and treatment of gynecological conditions. M. Woman's J. 54: 20-26, Oct., 1947.

Nolan, James F., & Stanbro, William [Mallinckrodt Inst. Radiol. & Wash. Univ. Sch. Med., St. Louis, Mo.]: Dosage calculations for various plans of intravaginal x-ray therapy. Radiology 49: 462-475, Oct., 1947.

Pratt, J. P. [Henry Ford Hosp., Detroit, Mich.]: Bleeding associated with the menopause. J. A. M. A. 135: 562-564, Nov. 1, 1947.

Wasson, W. Walter, & Greening, Roy [Denver, Colo.]: Further observations with intravaginal roentgen therapy of cancer of the female pelvis. Radiology 49: 452-461, Oct., 1947.

VULVA

Cunningham, Joseph A., & Hardy, Julian [Birmingham, Ala.]: Hidradenomas of the vulva. Report of four cases with an evaluation of them in the light of analogous breast lesions. South. Surgeon 13: 831-838, Nov., 1947.—Four vulval sweat-gland tumors are reported with special reference to their similarity clinically and histologically to the intraductal papillary tumors of the breast. The analogy between the breast and vulva is drawn—based on their similar embryologic origin.—Auth. Summ.

McKelvey, J. L. [Univ. Minn. M. Sch., Minneapolis, Minn.]: The treatment of carcinoma of the vulva. Am. J. Obst. & Gynec. 54: 626-635, Oct., 1947.

Miller, Norman F.; Parrott, Max H.; Stryker, Joan; Riley, Gardner M., & Curtis, Arthur C. [Univ. Mich., Ann Arbor, Mich.]: Leucoplakia of the vulva. Preliminary report. Am. J. Obst. & Gynec. 54: 543-560, Oct., 1947.—The patients were divided into two groups: prestudy—143 seen prior to July, 1945; study—36 subjected to careful scrutiny since January 1, 1946 (includes 25 patients from the prestudy category and 11 new patients seen in 1946). *Prestudy Group*: Average age was 55.6 yrs., range 23 to 80 yrs. One was pregnant. 94.2% were or had been married. 67.7% were parous; parity was unknown in 11.1%. Symptoms included pruritus vulvae (in 108, the most constant symptom), irritation and burning, vaginal discharge, dysuria, pruritus ani, vulvar pain, bleeding and dyspareunia. Treatment varied. Excision or vulvectomy was done in 54 cases, with 13 recurrences (24.7%). After treatment, 35.5% were moderately to greatly improved, 14.6% were unimproved, 11.1% died, 38.3% had no follow-up. The histologic appearance of the hypertrophic (leukoplakia) and the atrophic (kraurosis) phases of the condition is illustrated and discussed. *Study Group*: No apparent relationship of co-existing disease, blood pressure, the peripheral blood picture, and vaginal secretions to the vulvar lesions was found. Emotional instability may be a factor in aggravating and prolonging the pruritic phase, but a cause and effect relationship cannot be assumed as yet. The role of chronic irritation as an etiologic factor has not yet been evaluated. Of 25 studied for allergic manifestations, 14

(56%) had no such history, 11 (44%) had an allergic background (2 of these were somewhat relieved of pruritus after removal of the offending allergen). Blood-plasma vitamin-A determinations were made on 10 cases, 9 of which were within or above accepted limits of normal. Of 12, 6 revealed free HCl, 6 were achlorhydric. Blood-plasma ascorbic-acid levels were normal or higher in 14 of 22 patients. Urinary estrogen assay was normal or above in 22 (84%) of 26, and 23 had normal or above normal 17-ketostroid levels. Urinary follicle-stimulating hormone determinations made on 20 showed only 3 abnormal. As yet there is no entirely satisfactory cure for leukoplakia vulvac and the use of Alfa-Ray ointment, ascorbic acid, benadryl, chlorophyl ointment, lanolin, orctone, pyribenzamine and petroleum jelly have so far shown no real promise. No one remedy has been helpful for all patients. No surgery was performed on the study group, though the authors recognize its importance in treatment of malignant vulvar lesions.—*J. A. Chamberlin, M.D.*

Wilson, Karl M. [Univ. Rochester, N. Y.] *Melanoma of the vulva with report of two cases.* J. Mt. Sinai Hosp. 14: 688-694, Sept.-Oct., 1947.

CERVIX

Arneson, A. N. [Edward Mallinckrodt Inst. Radiol., Wash. Univ. Sch. Med., & Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: *Clinical diagnosis of carcinoma of the cervix.* Radiology 49: 400-402, Oct., 1947.

Ayre, J. Ernest [McGill Univ., Montreal, Quebec]: *Cervical cancer: a disordered growth response to inflammation in the presence of estrogen excess and nutritional deficiency. Cytological, clinical, nutritional, and pathologic studies.* Am. J. Obst. & Gynec. 54: 363-390, Sept., 1947.—Cytology studies have been found valuable in early diagnosis of cervical cancer and in estimating endogenous estrogen. Comparative vaginal and cervical cornification counts have revealed greater concentration of estrogens in the cervix in 87% of cases studied. Some degree of chronic cervicitis is believed to be present in 4 of 5 adult cervixes. Estrogen-fixation and concentration in infected cervical tissues is believed to be a growth-stimulating factor predisposing to cancer. Evidence of excessive tissue estrogen has been found in 92% of 50 cervical cancers. Deficient urinary thiamine excretion has been found in 86% of 50 cervical cancers. 10% of 50 controls showed the same deficiency. Riboflavin deficiency was found in 38.8% of cancer cases, and in 6.8% of the controls. Studies of cervical biopsies illustrating abnormal growth proliferation in the presence of cervicitis, excess tissue estrogens, and low thiamine excretion are presented. Partly by speculation, partly by interpretation of evidence presented, an attempt is made to correlate infection, excessive tissue estrogens, and nutritional deficiency in the production of cervical carcinoma of the squamous type. The possible concentra-

tion of estrogen around cervical cancer lesions arouses great hope for improved therapy with radioactive isotopes. Just as thyroid cancer may succumb to radioactivated iodine, so also may the selective affinity of estrogen for proliferating müllerian tissues enable successful treatment of cancer of the cervix.—*Auth. Summ.*

Bayer, Richard: *Die Wirkung der erzwungenen Hypoglykämie auf das Genitalkarzinom der Frau.* [The effect of forced hypoglycemia on carcinoma of the female genitalia.] Krebsarzt 2: 425-442, Oct., 1947.—A diabetic diet (vegetables, 400 gm. meat and 80 gm. oil [4 white bread units], with insulin, t.i.d., in increasing daily doses of from 4 to 68 units) was given 75 patients with cervical, and 7 with uterine carcinoma. The patients were either untreated or (16) previously treated with x-rays. Concomitant "Orthner" ligation of the hypogastric arteries was done in some. Cancer-tissue necrosis was visible by the 4th day, most marked in the primary tumor but exerting some effect on metastatic tissues. This was accentuated by Orthner's ligation which was performed on patients not primarily operable but in whom ligation would not possibly produce peritonitis. Treatment should not exceed 3 wks. and should be followed by a Freund-Kaminer diet.—*M.C.J.*

Behney, Charles A. [Univ. Pennsylvania, Philadelphia, Pa.]: *Transvaginal high voltage therapy for the treatment of carcinoma of the cervix.* S. Clin. North America 27: 1550-1554, Dec., 1947.

Bowen, Charles F. [Columbus, O.]: *Vaginal infections and cancer of the cervix.* Clin. Med. 54: 281-287, Sept., 1947.

Bowing, Harry H. [Mayo Clin., Rochester, Minn.]: *Intracavitary radium therapy for carcinoma of the uterine cervix.* Radiology 49: 406-410, Oct., 1947.—Intracavitary radium therapy has been used at the Mayo Clinic for 30 yrs. If all zones of the tumor are accessible, treatment is classified as complete and designed for cure; otherwise, as limited, for palliation. However, limited therapy may be extended according to subsequent indications. Radium therapy is usually administered with an applicator containing one or more platinum tubes of 50 mg. radium sulfate each. Doses of 300 to 400 mg. hrs. are applied in 3 to 24 hrs. every 1 to 7 days over a period of 10 to 21 days. Doses in mg. hrs. to the zones of the treatment area are: 2100 to the vaginal zone, 1400 to the distal cervical zone, and 2000 to 2400 to the intrauterine zone. All treatment is given with the patient in the knee-chest position, considered superior for visualization and more accurate irradiation of the lesion. Supplementary roentgen therapy, which overlaps radium therapy by a few days, consists of 500 r to 700 r (in air), produced by 200 kv. and filtered with 0.75 mm. Cu and 1.0 mm. Al, to 2 anterior and 2 posterior fields, repeated after 3 mos. 1450 cases were treated by this method between 1915 and 1929. Of 264 cases treated between 1915 and 1919, 14.4% were

living 3 or more yrs.; of 522, between 1920 and 1924, 35.4%; and of 585, between 1925 and 1929, 42.7%. Improvement is attributed to better visualization of the lesion and more accurate placement of the radium.

Data on followed cases revealed 69.2% of 13 cases with Stage-I lesions living 5 or more yrs.; 60.2% of 78 with Stage-II lesions; 29.7% of 753 with Stage-III lesions; and 6.5% of 138 with Stage-IV lesions. The importance of administering complete courses of treatment is stressed. 52.9% of 565 traced patients who received a complete course of radium therapy survived 3 or more yrs. compared with 21.4% of 739 traced patients who received limited therapy. The author emphasizes that radium technique must be flexible to produce the most benefit and contends that radium and roentgen therapy should be used in complementary fashion.—*S. A. Wilkins, M.D.*

Brewer, John I. [Chicago, Ill.]: Carcinoma of the cervix: radiological aspects. *Radiology* 49: 404-405, Oct., 1947.

Ernst, Edwin C. [Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: Improved methods of intravaginal roentgen and radium therapy in carcinoma of the cervix. *Radiology* 49: 425-428, Oct., 1947.—Two improved models of combination cervical radium applicators and expanding colpostats are reported. Each has a cervical stem, at the base of which is an expanding colpostat with 4 or more capsules or radiation centers. Once the cervical stem has been inserted, the colpostat is expanded by long applicator rods until the 7 to 9 vertical and horizontal radium sources are spread 1 cm. apart into the fornices and parametrium, thus more accurately placed and spaced than by other methods; neither tissue necrosis nor localized "hot spots" have been observed. The applicator can be introduced easily and quickly with less radiation exposure to the operator and assistants. Plastic translucent cones with lead-lined inserts are described for transvaginal x-ray therapy in cervical carcinoma. The cones can be heated and molded to the particular shape, size and diameter of the vaginal vault. Better visualization of the lesions is afforded and identification of landmarks helps to minimize overlapping of multiple fields. Adequate protection of adjacent structures is obtained by auxiliary metallic cones and lead inserts. Clinical studies over a 2-yr. period suggest the advantages of these methods but final evaluation is deferred.—*S. A. Wilkins, M.D.*

Glatthaar, E. [Univ.—Frauenklin. Zürich, Switz.]: Über Regeneration und Neoplasie an der Portio. [Regeneration and neoplasia of the cervix.] *Schweiz. Ztschr. f. Path. u. Bakt.* 10: 25-35, 1947.—A review. The study of the regeneration of the epithelium in the region of the external uterine orifice, the frequently atypical differentiation which takes place there during regeneration, has enlarged our insight into the genesis of carcinoma of the cervix. Recent experimental studies on the genesis of cancer are

in agreement with the view that cervical cancer results from the chronic action of nonspecific carcinogenic factors that induce and maintain an increased tissue regeneration.—*Auth. Summ.*

Goldberger, Morris A., & Mintz, Nathan [Mt. Sinai Hosp., New York, N. Y.]: Early carcinoma of the cervix; its pathological and clinical aspects. *J. Mt. Sinai Hosp.*, 14: 784-792, Sept.-Oct., 1947.

Grünberger, Viktor: Beitrag zu den Frühsymptomen des Kollumkarzinoms. [Early symptoms of carcinoma of the cervix.] *Krebsarzt* 2: 387-398, Sept., 1947.—A 3-yr. (1943-1945) statistical study of 222 cases is presented in great detail. Highlights are greatest frequency between 40-60 yrs. but range from 1 in early 20's to 1 in early 80's. Stage I, 46 (20.7%); II, 96 (43.3%); III, 80 (36%). Of 46 in I, 43 operable (97.4%); II, 81 (82.7%); III, 17 (21.2%). In I and II patients were inoperable because of heart disease, old age, etc.; III, usually carcinoma too far advanced. Incidence of stage III increased with increase in age. 109 (49.1%) presented themselves within a few days to 3 mos. of first symptoms observed: then in stage I, 25; II, 45; III, 39, of whom 29 were inoperable. First symptom: 180 (81.1%) hemorrhage—54.4% post-, 45.6% pre-menopausal; discharge, 126 (56.7%); loss of weight, 95 (42.8%); pain, 119 (53.6%). 180 had been pregnant one or more times. Of 193 studied histologically, 116 (60.1%) had squamous-cell carcinoma. Those seen after symptoms had been present 3 mos. were in Stage I, 62.5%; II, 42.5%; III, 46.6%. Of 149 who had seen a physician prior to coming to the Clinic, 88 were examined promptly. The other 61 were given all manner of treatments: drops, pills, physical therapy, etc.—*M.C.J.*

Grünberger, Viktor: Seltene Metastasenbildung nach operiertem Kollumkarzinom. [Rare location of metastases following carcinoma of the cervix removed operatively.] *Krebsarzt* 2: 459-465, Oct., 1947.

Gurskis, Eugenia E.; Beaver, Donald C., & Nelson, Harry M. [Woman's Hosp., Detroit, Mich.]: The microscopic criteria for the diagnosis of early carcinoma of the cervix uteri. *Surg., Gynec. & Obst.* 85: 727-733, Dec., 1947.

Harris, William, & Silverstone, Sidney M. [Mt. Sinai Hosp., New York, N. Y.]: Radiation therapy for cancer of the cervix with an analysis of the fundamental dosimetry. *J. Mt. Sinai Hosp.* 14: 369-382, Sept.-Oct., 1947.

Jenkinson, E. L.; Pirkey, E. L., & Hamernik, F. J. [St. Luke's Hosp., Chicago, Ill.]: Five-year end-results in the treatment of carcinoma of the uterine cervix. *Radiology* 49: 415-418, Oct., 1947.—Ninety-eight cases of squamous-cell carcinoma of the uterine cervix were treated between 1935 and 1941. The 5-yr. survival in 75 traced cases (76.5% of total) is 23 (30.6%); 7 (77%) in 9 cases with Stage-I lesions, 7 (87.5%) in 8 of Stage-II; 8 (26.6%)

in 30 of Stage-III; and 1 (3.5%) in 28 of Stage-IV. Treatment of the typical case is outlined. Almost all receive 3000 to 4000 mg. hrs. radium by the gynecologist 1 to 3 wks. before x-ray therapy is instituted. Via 3 anterior, 3 posterior portals and 1 anterior vaginal portal, 8800 r (measured in air) is given in doses of 200 r through one portal daily for a calculated tumor dose of 4800 r. The rays are produced with 200 kv. p. and a Thoracuss filter (0.25 mm. Cu, 0.45 mm. Sn, and 1.0 mm. Al) and an h.v.l. of 1.9 Cu used. In Stage-III and -IV lesions, an additional 4800 r is given after 6 mos.; complete hysterectomy is recommended in Stage-I and -II lesions without evidence of extension in the interval. The advantage of heavier filtration than is used in most clinics is suggested by a table of comparative results with different filters. Contact therapy, substituted for radium in 5 cases of this series, is preferred because of the ease of controlling penetration and directing the beam.—S. A. Wilkins, M.D.

Lampe, Isadore [Univ. Hosp., Ann Arbor, Mich.]: Some aspects of the results of radiation treatment of carcinoma of the cervix uteri. *Am. J. Roentgenol.* 58: 651-662, Nov., 1947.—The survival experience in carcinoma of the cervix uteri following radiation treatment at the University of Michigan, calculated on an "absolute" basis, is presented for each of the 12 yrs., 1932 to 1943, inclusive, by means of survival curves (total number of patients, 1225). Comparison of results for each of the 12 yrs., following elimination of the effect of variation in frequency distribution of anatomical extent by means of the so-called "standardized" survival curve, demonstrates the "absolute" 5-yr. survival percentage to have risen from 20-25% for the yrs. 1932 to 1935, inclusive, to above 40% for the yrs. 1938 and 1939. Study of the 4-, 3- and 2-yr. survival curves indicates that this gain is essentially maintained for the yrs. 1940 to 1942, inclusive.—*Auth. Summ.*

Mahnert, Alfons: Triasoperation: Neurotomie-Vasoligatur-Drüsenausträumung als Kombinationsoperation bei fortgeschrittenem Karzinom des Collumuteri. [Neuromy, vasoligation, and dissection of the lymph nodes as a combined operation in advanced carcinoma of the cervix.] *Krebsarzt* 2: 473-480, Nov., 1947.—Treatment included extraperitoneal pelvic sympathectomy, vasoligation and radical excision of iliac and other regional lymph nodes, even when not showing carcinomatous infiltration. (Chemotherapeutic irradiation and dietetic adjustments will be reported later.) Discharge and hemorrhage decreased, pain was mitigated provided the nerve plexuses were not already involved.—M. C. J.

Masson, James C., & Judd, David B. [Mayo Clin., Rochester, Minn.]: Epithelioma of the uterine cervix. *J. Mt. Sinai Hosp.* 14: 483-490, Sept.-Oct., 1947.—Carcinoma of the cervix is not seen any more frequently today than it was 25 yrs. ago; and the present increase in deaths from uterine cancer is real, not apparent.

Etiological factors are discussed. Histological appearance is of more prognostic value than the extent of local growth. Epidermoid carcinoma (90% of cervix cancers) has a graver prognosis than adenocarcinoma. 82% of cervix cancers are inoperable when first seen. The results following surgical resection plus irradiation are so good that further trial is justified in spite of the good results following irradiation alone. Even in small lesions only radical surgery is justified. The Wertheim technique is preferred to the Schauta vaginal operation. The Taussig operation is not used. Including hospital mortality, of 63 patients treated by Wertheim hysterectomy plus irradiation, 73% lived 5 yrs. as compared to 38.9% of 18 treated by operation alone. A course of irradiation is often given 6-8 wks. preoperatively. At operation the local lesion is destroyed by cautery or zinc chloride. Post-operative irradiation should always be given. If progress is to be made in treatment of cervix cancer, it will be the result of specific treatment not known today and will be prophylactic against predisposing factors.—D. A. S.

Miller, James Raglan [Hartford, Conn.]: A contribution to the technique of removing large cervical fibromyomas. *J. Mt. Sinai Hosp.* 14: 515-519, Sept.-Oct., 1947.—Six case reports.

Neary, G. J. [Mt. Vernon Hosp. & Radium Inst., Northwood, Middlesex, Eng.]: Physical aspects of intracavitary radium treatment of carcinoma of the cervix uteri. Part III. A new applicator. *Brit. J. Radiol.* 20: 454-469, Nov., 1947.

Parsons, Langdon [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.]: Cancer of the cervix. Observation on the effect of x-ray therapy on regional nodes. *S. Clin. North America* 27: 1231-1239, Oct., 1947.

Regato, J. A., del [Ellis Fischel State Cancer Hosp., Columbia, Mo.]: Transvaginal roentgen therapy in carcinoma of the cervix. *Radiology* 49: 413-414, Oct., 1947.

Scarborough, J. Elliott, & Brown, Robert L. [Emory Univ. Sch. Med., Atlanta, Ga.]: Carcinoma of the cervix. *J. M. A. Georgia* 36: 385-392, Oct., 1947.

Siebert, Walter J. [St. Louis, Mo.]: Pathologic aspects of carcinoma of the cervix uteri. *Radiology* 49: 403, Oct., 1947.

Simon, L. G. [South Norwalk, Conn.]: The management of cancer of the cervix uteri. *Connecticut State M. J.* 11: 741-742, Sept., 1947.

Speert, Harold [Roosevelt Hosp., New York, N. Y.]: Cervical cancer in young girls. *Am. J. Obst. & Gynec.* 54: 982-986, Dec., 1947.—Report of 2 cases: adenocarcinoma in a girl 12 yrs. of age, and epidermoid carcinoma in one 19 yrs. of age.

Turner, George [El Paso, Tex.]: Radiation treatment of cancer of the cervix. *Texas State J. Med.* 43: 452-457, Nov., 1947.

reason to believe that the results from primary surgery even in early cervical cancer would be superior to radiotherapy, which generally produces 65 to 80% 5-yr. cures.—*S. A. Wilkins, Jr., M.D.*

Holman, Albert W., & Schirmer, Elizabeth H. [Portland, Ore.]: The results of three five-year studies of hydatid mole and chorionepithelioma on the Pacific Coast. *West. J. Surg.* 55: 525-537, Oct., 1947.—A résumé of three 5-yr. studies based on questionnaires answered by surgeons and obstetricians having case history records of chorionepithelioma or hydatid moles: 426 hydatid moles, 107 chorionepitheliomas, 67 of which followed hydatid moles. [The authors did not themselves verify the diagnoses pathologically—in many instances no such examination was made, the diagnosis resting on pregnancy tests or clinical history. Perhaps this accounts for the large number of chorionepitheliomas listed and the reported low mortality—2% in the last 5-yr. study on 50 so-called cases of chorionepithelioma, a condition which has a known mortality of almost 100%.]—*D. A. S.*

Jones, Harold O. [Northwest. Univ., Chicago, Ill.]: Early diagnosis of carcinoma of the uterus—the physician's responsibility. *Texas State J. Med.* 43: 449-452, Nov., 1947.

Kamperman, George [Harper Hosp., Detroit, Mich.]: Carcinoma of uterine fundus. Treatment by hysterectomy with preoperative radiation with radium and supervoltage roentgen therapy, and postoperative radiation with supervoltage roentgen therapy. *J. Mt. Sinai Hosp.* 14: 401-417, Sept.-Oct., 1947.—Of 23 cases of carcinoma of the uterine fundus treated by hysterectomy, with pre- and postoperative supervoltage x-ray therapy, 2 showed evidence of recurrence within the 1st yr., and died during the 2d. Of those treated 5 or more yrs. ago, 90% survive free of recurrence (1 survived 8 yrs., then died after operation for carcinoma of the colon; because of its histologic and clinical characteristics, this is considered as a new primary carcinoma). Of all 23, 19 (91%) are free from recurrence, although about half are not yet among the 5-yr. survivals. All cases were early and grade I clinically (uterus about normal size). Microscopically, the series was about equally distributed among grades I, II, and III. Of grade I, survival was 100%; 1 each of grade II and III died of recurrence. There was no evidence that preoperative radiation caused adhesions in these cases.—*Auth. Concl.*

Klempner, Emanuel [New York, N. Y.]: Chorionepithelioma: hormonal studies and pathological findings. *J. Mt. Sinai Hosp.* 14: 793-797, Sept.-Oct., 1947.—Case report.

Mintz, Maurice E. [New York, N. Y.]: Uterus didelphys with endometrial polyp in left uterus. *J. Mt. Sinai Hosp.* 14: 807-808, Sept.-Oct., 1947.—Case report.

Novak, Emil [Baltimore, Md.]: Cancer of the uterus. *J. A. M. A.* 135: 199-206, Sept. 27,

1947.—No marked improvement in the control of cancer of the uterus has been achieved recently. In 1944 no less than 17,153 women died thereof compared with 16,516 in 1941. A growing conviction exists that the cause of cancer is intracellular not extrinsic, but that extrachromosomal factors do play some part. Probably the change affects a group of cells rather than a single cell and a common denominator is present. The genetic factor must be of considerable importance: in some it is so strongly developed that cancer will arise without extrinsic irritation: in others, only if an extrinsic factor is present as well; and in still others it will not arise regardless of the local irritation. The role of ovarian hormones in the genesis of cancer of the uterus is still unproved. As long as uncertainty exists, however, estrogen therapy should be held to a minimum or avoided in those with a hereditary tendency to cancer or who may be considered to have a predisposition because of other conditions such as late menopause, functional uterine bleeding, or endometrial hyperplasia.

Cervical carcinoma is a disease of long duration. The beginning stage, preinvasive carcinoma, is curable by simple complete excision; further study usually reveals definite invasive-ness. Colposcopic examination and the Schiller test have little value except that the latter may suggest points for biopsy when there is no gross lesion. The need for expert cytological examination is the chief disadvantage of the vaginal smear. It may be useful for screening, with a central agency for interpretation. Biopsy remains the most important diagnostic procedure. Treatment of cervical carcinoma is now passing into the phase of combined preliminary radiation and surgery for Stage I and II, with radiation alone for the more advanced. The plan of preliminary radiotherapy and the scope of radical surgery is still unsettled. A large cuff of vaginal mucosa should be removed because of frequent recurrence here. Meig's experiment of radical operation and extensive node dissection is laudable and the results will be of interest. Pelvic nodal involvement occurs in a high proportion of his series. This combined plan cannot be applied to more than 29%. Thus for the great majority radiotherapy remains the method of choice. Because of the marked variation in lesions classed as League of Nations I and II, a new subdivision is offered: Stage I(a), preinvasive lesions; Stage I(b), lesions not over 1 cm.; Stage I(c), lesions limited to the cervix but larger than 1 cm. Stage II, large lesions of part, or of the whole, of the cervix with moderate vaginal or parametrial infiltration. Stages III and IV, as they are. Because of the relative ease of estimation, vaginal and parametrial infiltration is a more useful index of clinical stage than pelvic lymph-node involvement. The generally accepted treatment of corporeal carcinoma is combined surgery and radiotherapy, panhysterectomy being the more important part. Preliminary radiation lessens the hazard of operative procedures and improves the final results but introduces a delay of 6 to 8 weeks.

Cancer detection clinics serve a useful func-

- tion by creating wide interest among women and ensuring a competent gynecologic examination every six months so that the early lesions may be detected in a highly curable stage. An increase in the physician's feeling of personal responsibility to his patient would decrease the delays in early diagnosis.—*M. W. Stearns, M.D.*
- Odell, Lester D., & Scott, Joseph [Univ. Hosps., Univ. Iowa, Iowa City, Iowa]: An inquiry into the causes for bleeding from uterine myomata. *J. Kansas M. Soc.* 48: 537-540, Dec., 1947.
- Oosterhagen, P. H. [Pretoria, S. Africa]: Carcinoma of the corpus uteri. *South African M. J.* 21: 864-866, Nov. 22, 1947.
- Pearson, Homer L. [Miami, Fla.]: Multiple carcinomata of the uterus. *South. M. J.* 40: 728-732, Sept., 1947. Case of coexisting squamous carcinoma of cervix and adenocarcinoma of corpus uteri.
- Schinkele, Otto [Univ.-Frauenklinik, Vienna, Austria]: Ein Angiomyom des Endometriums. [An angiomyoma of the endometrium.] *Wien. klin. Wchnschr.* 59: 617-618, Sept. 19, 1947.
- Toppozada, H. K. [Farouk I Univ. Hosps., Alexandria, Egypt]: Cystic degeneration of uterine fibromyomata. Report of a case. *J. Roy. Egyptian M. A.* 30: 476-481, Oct., 1947.
- ### OVARY AND FALLOPIAN TUBE
- Andrews, C. J. [Norfolk, Va.]: Krukenberg tumor, primary. Follow-up report. *South. M. J.* 40: 869-870, Oct., 1947.
- Bickers, William; Sahyoun, Philip, & Saadeh, Arif [Am. Univ. Beirut, Syria]: Granulosa cell tumor of the ovary. *Virginia M. Monthly* 74: 509-512, Nov., 1947 - Two case reports.
- Cavanagh, Harold N. [DeCourcey Clin., Cincinnati, Ohio]: Dysgerminoma of ovary. *Am. J. Surg.* 74: 854-855, Dec., 1947 - Case report.
- Hardy, Julian P., & Toole, Arthur F. [Birmingham & Talladega, Ala.]: Arrhenoblastoma. With case report. *J. M. A. State Ala.* 17: 125-128, Oct., 1947.
- Hartley, R. L. [Univ. Liverpool, Eng.]: Ovarian tumours. *M. Press* 218: 241-245, Sept. 19, 1947.—A review.
- Jennings, W. L. [Daytona Beach, Fla.]: Masculinizing tumor of the ovary. Report of a case. *J. Florida M. A.* 34: 160-161, Sept., 1947.
- Kriss, Bruno R. [New York, N. Y.]: Neoplasm of a supernumerary ovary. Report of two cases. *J. Mt. Sinai Hosp.* 14: 798-801, Sept.-Oct., 1947.
- Lösch, W.: Über das maligne Chorionepitheliom der Tube. [Malignant chorionepithelioma of the tube.] *Krebsarzt* 2: 449-459, Oct., 1947.—Report of 2 cases.
- Marek, Charles B., & Phillips, Malcolm D. [Harford Mem. Hosp., Havre de Grace, Md.]: Dysgerminoma of the ovary in a 7-year-old child. *Am. J. Obst. & Gynec.* 54: 893-894, Nov., 1947.
- Miller, Arthur; Grayzel, David M.; Schiffer, Mortimer, & Rosenblatt, Philip [Jewish Hosp. Brooklyn, N. Y.]: Adenocarcinoma arising in an endometrial cyst of the ovary. *Am. J. Obst. & Gynec.* 54: 1022-1027, Dec., 1947.—Case report and review of the literature.
- Nora, Ernest D., & Davison, Richard M. [Chicago, Ill.]: Pleurisy with effusion associated with pseudomucinous cystadenoma. (Meigs' syndrome). *Dis. of Chest* 13: 423-435, Sept.-Oct., 1947. Case report and survey of the literature.
- Novak, Emil [Johns Hopkins M. Sch., Baltimore, Md.]: Adenocarcinoma of ovary arising from endometrial cyst, with report of a case. *J. Mt. Sinai Hosp.* 14: 529-533, Sept.-Oct., 1947.
- Poole, Charles S. [Mt. Sinai Hosp., New York, N. Y.]: Ruptured dermoid cyst. Case report. *J. Mt. Sinai Hosp.* 14: 809-811, Sept.-Oct., 1947.
- Quinland, William S., & St. Hill, Ian R. [McHarry M. Coll., Nashville, Tenn.]: Cystic teratoma (dermoid cyst) of the ovary. A study of 52 cases. *South. M. J.* 40: 908-914, Nov., 1947.
- Ragins, Alex. B., & Craue, Robert D. [Cook County Hosp., Chicago, Ill.]: Cavernous hemangioma of the fallopian tube. *Am. J. Obst. & Gynec.* 54: 883-886, Nov., 1947.—A case of cavernous hemangioma of the fallopian tube is reported, the first to appear in the literature. A brief discussion of the pathogenesis indicates the lesion is a true neoplasm.—*Auth. Summ.*
- Roper, C. J. [Jasper, Ga.]: Arrhenoblastoma. *J. M. A. Georgia* 36: 393-394, Oct., 1947.—Case report.
- Sorasto, U.: Synnytyksen aiheuttama harvinaisten munasarjakasvaimen repeäminen. [An unusual occurrence of rupture of an ovarian tumor (dermoid cyst) in the course of parturition.] *Duodecim* 63: 757-767, 1947.
- ### GENITOURINARY TRACT
- Dant, Richard V., & McDonald, John R. [Mayo Clin., Rochester, Minn.]: Diagnosis of malignant lesions of the urinary tract by means of microscopic examination of centrifuged urinary sediment. *Proc. Staff Meet., Mayo Clin.* 22: 382-386, Sept. 3, 1947.—Preliminary report. Techniques are presented for cytologic study of urinary sediment. 10 to 20 cc. of urine are collected in equal amount of 95% alcohol. This is centrifuged for 5 minutes at 15,000 and the supernatant fluid decanted. For staining with methylene blue the sediment is spread on a slide, allowed to dry, then Terry's polychrome methylene blue applied lightly with a glass rod.

The slide is rinsed in 1% sodium chloride and mounted in Brun's glucose-glycerin-camphor medium. For staining with the Papanicolaou technique the slides are prepared with egg albumin. For fat staining with Sudan IV, the urine is collected without alcohol and the smears are fixed in 10% formalin. The cytologic criteria for the identification of cancer cells is based on (1) the nucleus (size, anisonucleosis, poikilonucleosis, hyperchromatosis, fragmentation, multiplicity) (2) the nucleolus (multiplicity, variations of size, hyperchromatosis) and (3) the cytoplasm (fat-filled, basophilic reactions). Photomicrographs of urinary sediment containing cells of carcinoma of the prostate and carcinoma of the bladder are shown.—*J. P. Wozencraft, M.D.*

Kittredge, W. E.; Henthorne, John C., & Whitehead, Mark [Tulane Univ. Sch. Med. & Ochsner Clin., New Orleans, La.]: Glandular metastatic malignancy in the urinary tract. Report of 4 cases. *J. Urol.* 58: 282-288, Oct., 1947.—Four cases of glandular carcinoma of the urinary tract, illustrating the difficulty of determining whether an adenocarcinoma is primary or secondary in this location, have been reported. In 1, the tumor of the bladder was probably metastatic from a carcinoma of the colon. In 2, the adenocarcinoma probably arose from plaques of urinary tract epithelium which had undergone metaplasia to the secretory type. In 1, metaplasia of the epithelium to the secretory type evidently occurred in an infiltrating transitional-cell carcinoma.—*Auth. Summ.*

KIDNEY

Beretervide, Enrique A., & Reboiras, J. J. [Ramos Mejía Hosp.]: Radioterapia y nefrectomía asociadas in el tratamiento de un adenosarcoma de riñón. Curación aparente a los 5 años. [Radiotherapy and nephrectomy in the treatment of an adenocarcinoma of the kidney. Apparent cure for 5 years.] *Arch. argent. de pediat.* 18: 145-158, Sept., 1947.—Case report. Fibromyoblastic adenocarcinoma.

Burgess, C. M. [The Clinic, Honolulu, Hawaii]: Wilms's tumor: report of three year cure. *J. Urol.* 58: 412-416, Dec., 1947.

DeMuylder, Charles G. [Louvain, Belgium]: Neutrogenesis observed in a mixed Grawitz-Wilms tumor. *Arch. Path.* 44: 451-458, Nov., 1947.

DeWan, Charles H., & Meltzer, Saul B. [Guthrie Clin., Sayre, Pa.]: Primary renal neoplasms. *Guthrie Clin. Bull.* 17: 90-95, Oct., 1947.

Eskersky, Gerry L.; Saffer, Sidney H.; Panoff, Charles E., & Jacobi, Mendel [Beth-El Hosp., Brooklyn, N. Y.]: Wilms's tumor in the adult: review of literature and report of three additional cases. *J. Urol.* 58: 397-411, Dec., 1947.

Lazarus, Joseph A., & Marks, Morris S. [New York, N. Y.]: Renal hemangioma. *Urol. &*

Cutan. Rev. 51: 500-509, Sept., 1947.—Case report & review of literature.

Lownes, John B.; Baron Samuel, & Lipschutz, Harold [Jewish Hosp., Philadelphia, Pa.]: Hemangioma of the kidney: report of two cases. *J. Urol.* 58: 417-423, Dec., 1947.

Ludden, T. E., & McDonald, John R. [Mayo Clin., Rochester, Minn.]: Diagnosis of tumors of the kidney by cytologic investigation of urinary sediment. *Proc. Staff Meet., Mayo Clin.* 22: 386-390, Sept. 3, 1947.—Preliminary report. Cancer cells were found in the urinary sediment prior to operation in 2 cases of papillary carcinoma of the renal pelvis proved by operation. A photomicrograph of a hypernephroma cell in the urinary sediment is shown. The most useful cytologic criteria of malignancy are increase in the size of nuclei in proportion to size of cells and hyperchromasia of nuclei.—*J. P. Wozencraft, M.D.*

URETER : BLADDER : URETHRA

Allen, Edgar V.; Pratt, Joseph Hyde, & Thompson, Gershom J. [Mayo Clin., Rochester, Minn.]: Segmental compression of iliac artery by a metastatic malignant lesion: report of a case. *Proc. Staff Meet., Mayo Clin.* 22: 525-526, Nov. 12, 1947.—Presumably primary carcinoma of the bladder.

Barringer, Benjamin S. [New York, N. Y.]: Twenty-five years of radon treatment of cancer of the bladder. *J.A.M.A.* 135: 616-618, Nov. 8, 1947.—This study is based on 298 personal patients, whose vesical cancers were believed to be confined to the bladder, and who were treated with radium. 255 were histologically diagnosed as cancer (incl. 7 with atypical papilloma classified by the author with papillary carcinoma); 43 had inadequate pathological reports. There were 35.7% 5-yr. cures in these 255 cases; in 113 graded cases, the 5-yr. cures were: 55%, grade I; 32%, grade II; 11%, grades III and IV combined. In tumors graded by pathological examination modified by the clinical estimate, there were 52% 5-yr. cures in papillary cancers and 23% 5-yr. cures in infiltrating cancers. Screened radon seeds of 1.5 mc. (placed about 0.75 cm. apart, implanted throughout the tumor, extending to its edge, at a depth determined by the estimated degree of infiltration) were used in all vesical cancers incl. papilloma with atypical cells in which the tumor was in or on the trigone or ureteral orifices or internal urethra. Seeds were inserted near a ureteral orifice without hesitation, although the possibility of resultant ureteral narrowing had to be kept in mind.

The need for careful follow-up for the treatment of the complications of radium therapy and the need to distinguish between living tumor, stone formation, and postradium slough are pointed out. Partial bladder excision was reserved for cancers involving the vault; total cystectomy, for tumors having multiple points of origin in the bladder. Large single infiltrative

cancers occupying a large part of the bladder and extending to the vesical base were usually considered incurable by any type of treatment. The importance of complete clinical examination of the tumor in conjunction with the pathological examination is stressed.—*W. F. Whitmore, M.D.*

[In the "Abstract of Discussion" (pp. 621-622), Barringer (Attending Surgeon, Urological Service, Memorial Hospital until 1942) referring to Marshall's paper, "A Comparison of Radiation and Surgery for Cancer of the Bladder," (*J.A.M.A.* 134: 501-507, June 7, 1947) says, "I doubt the accuracy of his published results." Marshall's paper shows that of 300 consecutive cases of bladder cancer treated at the New York and Memorial Hospitals from 1932 to 1938, incl., only 6% of the irradiated cases were free of tumor at 5 yrs., and only 17.5% survived 5 yrs.; there was no spontaneous disappearance of untreated cancer although about 10% might survive 5 yrs. Approximately 80% of those irradiated die within 5 yrs., in contrast to 90% of those not treated. Morbidity in both the treated and untreated series was decidedly high. The average survival of those irradiated was 24.5 mos.; of those untreated, 18.8 mos.—in comparison to a life expectancy of about 15 yrs. in the same age group of the general population. All the untreated patients must have died with cancer, although not necessarily of carcinomatosis. In 43% of the autopsies of irradiated patients, metastases were not sufficiently developed to be discovered—indicating that they did not die of carcinomatosis, but primarily of sepsis and upper urinary-tract obstruction. The survival rate among those irradiated was better when the cancer graded 1 or 2 (although less than half lived 3 yrs.) than when it graded 3 or 4. A small number of 10-yr. survivals indicated that irradiation may cure cancer of the bladder, although such results are uncommon. All treated tumors received radon-seed implantation with or without additional external irradiation. Occasionally irradiation was omitted but it was considered the treatment of choice, and enthusiasm for it was high. The lesions were all proved neoplastic by biopsy. Cases of papilloma were excluded, although a few with atypical features may have crept into the group classified as cancer. (Results of treatment of bladder cancer by fulguration, segmental resection, and total cystectomy with diversion of the urinary stream were briefly discussed. A small and recent series having had segmental resection was presented as well as a group of patients having had uretero-intestinal anastomosis and total cystectomy.)

Barringer's criticisms of Marshall's article are: (1) The variety of treatment received by the patients in Marshall's series: Some patients were treated with radium, some with external irradiation, some with both, some with neither. Marshall makes note of this in his paper; a recheck of the 1932-1938 vesical cancer cases at Memorial Hospital by the professional statistician shows that 91.3% received irradiation. (2) The possible presence of some atypical papil-

omas in Marshall's series: This is acknowledged, although Marshall made efforts to exclude all cases except cancer. However, the inclusion of papillomas would tend to improve over-all results. (3) The fact that Marshall personally treated none of these cases: Marshall, having treated none of the cases personally, might be considered to be in an ideal position for compiling the results objectively. (4) The incorporation of Barringer's private cases in Marshall's statistics: For many years it has been the policy of Memorial Hospital to make available, for study by all staff members, records of all private cases in its files.

Barringer's cases are drawn from 25 yrs. of radon treatment of cancer of the bladder: Marshall's cases from the years 1932-1938, inclusive. (The comparable number of cases in the two series, 298 and 300, respectively, is purely coincidental.) Barringer's series is composed of personal cases in which the tumor was believed to be confined to the bladder; Marshall's series is composed of unselected and consecutive cases of bladder cancer and includes many palliatively treated and far advanced cases. There would seem to be little basis for attempting to compare or reconcile two so widely divergent papers.

Through the courtesy of Dr. Allen O. Whipple, Clinical Director of Memorial Hospital, the following compilation by the Statistics Department of Memorial Hospital has verified Marshall's figures:

Department of Statistics
Memorial Hospital
Five-Year End Results

This series consists of all cases of cancer of the bladder, unselected and consecutive, early and advanced, admitted to Memorial Hospital during the years 1932-1938, inclusive. All patients reported as cured have been proved microscopically to have cancer. Lack of pathological proof does not exclude failures.

<i>Total Number of Patients Admitted</i>	254
Indeterminate Group	26
Determinate Group	228
Total Number of Failures in Treatment	214
Free from Cancer at Five Years or More	14
Net Five-Year Successful End Results	14/228 = 6.1%
Five-Year Survivals:	
Total patients surviving five years or more	32
Five-Year Survival Rate ..	32/228 = 14.0%

Barringer is entitled to his opinion regarding the significance of Marshall's figures; but the fact that Marshall's cure rate is 0.1% less and his survival rate 3% more than those of the professional statistician is hardly a major inaccuracy.]

Baurys, William, & Manley, R. Maxwell [Guthrie Clin., Sayre, Pa.]: *Primary carcinoma of the*

- ureter. With a case report. *Guthrie Clin. Bull.* 17: 72-79, Oct., 1947.
- Dreiling, David A., & Hyman, A. [Mt. Sinai Hosp., New York, N. Y.]: Hysterectomy and total cystectomy with bilateral ureterocutaneous implantation for carcinoma of the bladder. Secondary ureterosigmoidal anastomosis for complicating ureterovaginal fistula. *J. Urol.* 58: 435-440, Dec., 1947.—Case report.
- Fort, Adolfo: Carcinoma polimorfo de la vejiga. (Polymorphous carcinoma of the bladder.) *An. de cir. [Argentina]*: 12: 272-277, Sept., 1947.—Case report. Primarily adenocarcinoma.
- Higgins, Charles C. [Cleveland Clin., Cleveland, O.]: Total cystectomy for carcinoma of the bladder. *J. A. M. A.* 135: 619-622, Nov. 8, 1947.
- Hindley, J. Mason, Jr., & Hunter, James S., Jr. [Univ. Md. Sch. Med., Baltimore, Md.]: Primary carcinoma of the ureter: presentation of a case. *J. Urol.* 58: 176-181, Sept., 1947.
- Kretschmer, Herman L. [Chicago, Ill.]: Rhabdomyosarcoma of the bladder. Report of a case and review of the literature. *Arch. Path.* 44: 350-355, Oct., 1947.
- Lenz, M.; Cahill, G. F.; Melicow, M. M., & Donlon, C. P. [New York, N. Y.]: The treatment of cancer of the bladder by radium needles. *Am. J. Roentgenol.* 58: 486-492, Oct., 1947.—Forty-four patients with microscopically proved cancer of the urinary bladder in or near the trigone were treated 5 to 15 yrs. ago with suprapubic cystostomy and implantation of radium needles. 34 died presumably of persisting or recurring cancer, and 1 died 15 yrs. after treatment, no cancer being found at autopsy. 9 patients are living, and appear free from clinical evidence of cancer. Extensions outside the bladder wall and involvement of the ureters were signs of poor prognosis. Results were best in small papillary tumors, though some of the larger infiltrating cancers responded well to the treatment. A tumor dose of 8000 γ r seems preferable to smaller doses.—*Auth. Summ.*
- Lower, William E., & Hausfeld, K. F. [Cleveland Clin., Cleveland, O.]: Primary carcinoma of the male urethra: report of 10 cases. *J. Urol.* 58: 192-206, Sept., 1947.
- Marshall, Victor F. [Cornell Univ. M. Coll.: N. Y., & Mem. Hosps., New York, N. Y.]: Transplantation of the ureters and total cystectomy. *J. Urol.* 58: 244-249, Oct., 1947.
- Pilcher, Frederick [Calgary, Alta.]: Primary carcinoma of the ureter. *Canadian M. A. J.* 57: 240-243, Sept., 1947. Report of 3 cases.
- Sammel, Eric [Johannesburg, S. Africa]: The radiological features of vesical leiomyoma and leiomyosarcoma. Case report. *Brit. J. Radiol.* 20: 423-425, Oct., 1947.
- Torres, Luis F., & Chikiamco, Paterno S. [Coll. Med., Univ. Penn. & Phil. Gen. Hosp.]: Transurethral resection and deep x-ray therapy in the surgical management of cancer of the bladder. *J. Philippine M. A.* 23: 453-454, Oct., 1947.
- Vallett, Brice S. [Wilmington, Del.]: Uretero-intestinal anastomosis with total cystectomy in vesical carcinoma. *Delaware State M. J.* 19: 194-197, Oct., 1947.
- Walker, Kenneth: The treatment of inoperable vesical carcinoma. *M. World [London]* 67: 428-430, Nov. 28, 1947.
- Ward, R. Ogier, et al.: The treatment of serious tumours of the bladder. *Brit. J. Urol.* 19: 144-171, Sept., 1947.—Symposium at Annual Meeting of the British Association of Urological Surgeons.
- Zaslow, Jerry, & Priestley, James T. [Mayo Clin., Rochester, Minn.]: Primary carcinoma of the male urethra. *J. Urol.* 58: 207-211, Sept., 1947.

PROSTATE

- Baines, G. H. [Birmingham United Hosp., Ala.]: Carcinoma of the prostate. *Birmingham M. Rev.* 15: 177-181, Oct., 1947.
- Birdsall, Joseph C.: Carcinoma of the prostate with an evaluation of its present day management. *Philadelphia Med.* 43: 197, 199, Sept. 27, 1947.
- Buehert, Walter I.: Culp, David A., & Jones, George H. [Geisinger Mem. Hosp., Danville, Pa.]: Carcinoma of the prostate gland. An analysis of 135 consecutive cases. *Pennsylvania M. J.* 51: 165-173, Nov., 1947.
- Charlewood, G. P. [Ajmer, India]: Complete prostatectomy. *Brit. M. J.* 2: 508, Sept. 27, 1947.—Case report.
- Colby, Fletcher H. [Mass. Gen. Hosp., Boston, Mass.]: Carcinoma of the prostate: total perineal prostatectomy. *S. Clin. North America* 27: 1307-1311, Oct., 1947.
- Cox, H. T. [Withington Hosp., Manchester, Eng.]: Adrenalectomy and prostatic carcinoma. Report of three cases. *Lancet* 2: 425-426, Sept. 20, 1947.—Three cases of carcinoma of prostate with marked secondary involvement were treated with stilbesterol and when no further palliation was obtainable adrenalectomy was performed. This seemed the obvious next step since the testes and the adrenal cortex have a similar embryological origin. In the first case, the patient died a few hours after left adrenalectomy. In the second, left adrenalectomy was followed by rise of 17-ketosteroid excretion and no clinical improvement. Operation on the right adrenal was refused. The third case had both adrenals removed at separate operations. Marked improvement followed the first operation, with progress from a paraplegic state to being able to walk

short distances. There was diminution of symptoms to a lesser degree following removal of the other adrenal. Each period of improvement was accompanied by a fall in 17-ketosteroid excretion. The author concludes that on present evidence adrenalectomy may be dismissed as a practical measure. The remissions and relapses in the third case, with determining changes in urinary 17-ketosteroids clearly demonstrate the sensitivity of the prostate carcinoma to ketosteroids of adrenal origin.—*A. G. James, M.D.*

Culver, Harry, & Baker, William J. [Northwest. Univ. M. Sch.; St. Luke's Hosp., and Cook County Hosp., Chicago, Ill.]: Carcinoma of the prostate gland. *Illinois M. J.* 92: 282-292, Nov., 1947.—Twelve case reports.

Fullilove, Robert E. [Flint Goodrich Hosp., New Orleans, La.]: Modern methods of treating carcinoma of the prostate. *J. Nat. M. A.* 39: 185-195, Sept. 1947.

Goodyear, William E. [Emory Univ. Sch. Med., Atlanta, Ga.]: Perineal prostatectomy; a hope for cancer cure. *J. M. A. Georgia* 36: 425-428, Nov., 1947.

Henline, Roy B. [N. Y. Hosp., New York, N. Y.]: Prostatic disease—with special reference to early diagnosis and treatment of carcinoma of the prostate. *New York Med.* 3: 17-20, 44, Nov. 5, 1947.

Hinnian, Frank [San Francisco, Calif.]: The obstructive prostate. *J. A. M. A.* 135: 136-141, Sept. 20, 1947.

Lubin, E. N.; Fetter, Theodore R., & Erf, Lowell A. [Jefferson M. C. Hosp., Phila., Pa.]: Subacute monocytic leukemia presenting symptoms of prostatism: a case report. *J. Urol.* 58: 272-276, Oct., 1947.—Another case of monocytic leukemia is presented; the 2d known case in which the presenting symptoms were those of prostatic urinary obstruction. The repeated episodes of complete urinary retention can be explained on the basis of recurrent exacerbations of edema of the prostate secondary to the leukemic infiltration. Alleviation of the obstructive symptoms by cystostomy, if transurethral electroresection is impractical, is indicated in such cases.—*Auth. Summ.*

Michon, P.; Guillemin, A., et Cayotte, J.: Implantations d'hormones complémentaires. Essais de traitement du cancer prostatique par implantation d'oestradiol. [Implantation of complementary hormones. An attempt to treat cancer of the prostate by implantation of estradiol.] *Bull. et mém. Soc. méd. d. hôp. de Paris* 63: 794-797, Oct. 10, 17, 1947.—Estradiol, 25 mg., was implanted in each of 5 patients with large carcinomas of the prostate. There was marked general improvement within 1 or 2 mos. although the prostate was not affected (to palpation). Estradiol was well tolerated.—*M. C. J.*

Neuswanger, C. H. [Waterbury, Conn.]: Cancer of the prostate. *Connecticut State M. J.* 11: 813-814, Oct., 1947.

Stettbacher, H. J. [Waterbury, Conn.]: Carcinoma of prostate. *Waterbury Hospital 1932 to 1946 inclusive. Connecticut State M. J.* 11: 814-816, Oct., 1947.

Wattenberg, Carl A. [Washington Univ. Sch. Med., Barnes Hosp., St. Louis, Mo.]: Bone changes and variations in skeletal metastases due to diethylstilbestrol and orchietomy during treatment of cancer of the prostate. *J. Urol.* 58: 378-383, Nov., 1947.

HEMATOPOIETIC SYSTEM

Barnard, Robert D. [New York, N. Y.]: Massive plasma transfusion and the pathodynamics of acute leukemia. *M. Rec.* 160: 610-612, Oct., 1947.—The good effects of plasma may be due to the plasma cholinesterase content.—*From Auth. Summ.*

Barnard, Robert D. [Laurelton, L. I., N. Y.]: The nature of acute leukemia and the interrelationship of the malignant dyscrasias. *New York State J. Med.* 47: 2703-2706, Dec. 15, 1947.

Bernard, A. [Soc. Méd. & Anat.-Clin. Lille]: Traitement d'une leucémie myeloïde par l'uréthane. [Urethane treatment of myeloid leukemia.] *J. sc. méd., Lille* 65: 496-498, Oct. 26, 1947.—Case report.

Bessis, et Bernard, Jean: À propos du traitement de la leucémie aiguë par exsanguino-transfusion. [Treatment of leukemia by exsanguination-transfusion.] *Bull. Acad. nat. de méd.* 131: 615-619, Nov. 4, 18, 1947.—A child 6½ yrs., preagonal on admission, was given an exsanguination transfusion of 800 gm.; 4 days later, one of 3.5 l.; 17 days later, 3.5 l., all by direct arm-to-arm method. There was immediate improvement. Four days after last transfusion both blood and bone marrow were normal microscopically.—*M. C. J.*

Brick, Irving B., & Greenfield, Maurice [M. C., A. U. S.]: Reticulum cell sarcoma with cardiac metastasis. Report of two cases with ante-mortem diagnosis of one. *Am. Heart J.* 34: 599-611, Oct., 1947.

Caussade, L.; Florentin, P.; Chalmot, P., & Michon, P.: Maladie de Hodgkin a type initial d'ictère hémolytique et caractères histologiques aberrants. [Hodgkin's disease beginning with hemolytic jaundice and atypical histological characteristics.] *Rev. méd. Nancy* 72: 251-255, Aug.-Sept., 1947.

Fontan, [A.]; Verger, P., & Verger, P.: Leucémie aiguë chez un garçon de 12 ans avec tumeur du médiastin. [Acute leukemia, with mediastinal tumor, in a twelve-year-old boy.] *J. méd. Bordeaux* 124: 410-413, Sept., 1947.

Gordon, Hugh W. [Eng.]: Mycosis fungoides. *Proc. Roy. Soc. Med.* 40: 700-701, Oct., 1947.

Hentsell, Henry H.; Tober, Jerome N., & Newman, Ben A. [Cedars of Lebanon Hosp., Los

- Angeles, Calif.]: The influence of nitrogen mustard on mycosis fungoides. Observations relating its effect to the reticulo-endothelial system. Blood 2: 564-577, Nov., 1947.—Since mycosis fungoides is considered a reticulo-endothelial disease, it is classified as a lymphoblastoma. In these, nitrogen mustard (methyl-bis [β -chloroethyl] amine hydrochloride) is known to effect transient palliative control. 4 of 6 cases of radioresistant mycosis fungoides showed a rapid and excellent, 2 a slightly delayed and only fair response to the drug. Clinical remission was manifested by diminution to complete clearance of pruritus and temporary involution of the infiltrative cutaneous lesions. Remissions were short-lived. The drug was used in various combinations with x-rays, colchicine and x-rays, and urethane and x-rays. Serial biopsies showed that those lesions with high incidence of reticulo-endothelial cells were most sensitive to nitrogen mustard. Nausea, vomiting, leukopenia were the most frequently noted toxic manifestations. [No definite dosage schedule related to weight is indicated.]—*H. D. Diamond, M.D.*
- Hettig, Robert A. [Houston, Tex.]: Recent advances in treatment of the leukemias and the lymphomas. Texas State J. Med. 43: 439-442, Nov., 1947.—Four case reports.
- Kierland, Robert R.; Watkins, Charles H., & Shullenberger, C. C. [Mayo Clin., Rochester, Minn.]: The use of nitrogen mustard in the treatment of mycosis fungoides. J. Investigative Dermat. 9: 195-201, Oct., 1947.—Methyl-bis (β -chloroethyl) amine hydrochloride (nitrogen mustard) was used in the treatment of mycosis fungoides in 6 patients. In 4 the condition had become resistant to x-ray therapy. 1 died of apparently unrelated causes shortly after a course of nitrogen mustard was given. The general condition and the cutaneous lesions of the other 5 patients improved significantly after treatment. 3 patients have had 2 courses of the drug. The duration of remissions is impossible to predict but in 1 patient a remission of more than 4 mos. duration has been obtained. Reactions are frequent, acute and occasionally severe; but in all cases it was possible to complete a course of therapy without serious ill-effects. The limited histopathologic findings indicate to us that the response of the individual lesions in the same individual and of lesions of different individuals to therapy with nitrogen mustard will vary greatly. Nitrogen mustard in the treatment of mycosis fungoides is an adjunct to previously recognized therapeutic measures and is of particular value when roentgen therapy is no longer of benefit.—*Auth. Summ. & Concl.*
- Landry, Benedict B., & Nolan, John O'L. [St. Francis Hosp., Hartford, Conn.]: Acute appendicitis in myelogenous leukemia—a case report. Connecticut State M. J. 11: 897-899, Nov., 1947.
- Lauckner, J. R., & Hebbert, F. J. [Stobhill Hosp., Glasgow, Scotland]: Suprarenal haemorrhage in monocytic leukaemia: with report of a fatal case. Glasgow M. J. 28: 366-373, Nov., 1947.
- Li, Jonah G.; McBride, Alice, & Mettler, Stacy R. [Univ. Calif. M. Sch., San Francisco, Calif.]: The co-existence of chronic leukemia and pregnancy. Blood 2: 592-596, Nov., 1947.—Case report.
- McAlister, John P. [Camden, Ark.]: Leukemia treated with urethane. J. Arkansas M. Soc. 44: 139-140, Nov., 1947.—Case report.
- Manning, Isaac Hall [Durham, N. C.]: The diagnostic value of the sternal bone marrow puncture in polycythemia vera. Am. J. M. Sc. 214: 469-475, Nov., 1947.
- Mathis, A. [Wien. Städt. Allg. Poliklin., Austria]: Zur Kasuistik der Polyzythämie mit Übergang in Leukämie. [Polycythemia passing into leukemia.] Wien. Zeitschr. inn. Med. 28: 392-397, Sept., 1947.—Case report: polycythemia which ended in acute myeloblastic leukemia.
- Miller, Franklin R. [Jefferson M. Coll. Hosp., Phila., Pa.]: The treatment of leukemia. Pennsylvania M. J. 50: 1331-1333, Sept., 1947.
- Philpott, O. S.; Woodburne, A. R., & Waldriff, G. A. [Univ. Colo. Sch. Med., Denver, Colo.]: Nitrogen mustard in the treatment of mycosis fungoides. J. A. M. A. 135: 631-633, Nov. 8, 1947.—Case report.
- Price, L. Woodhouse [Roy. Cancer Hosp., London, Eng.]: The pathology of lymph node enlargement. Post-Grad. M. J. 23: 401-425, Sept., 1947.
- Rüttner, J. R., & Albertini, A. v. [Univ. Zürich, Switz.]: Das grossfollikuläre Lymphoblastom. (Giant follicular lymphoblastoma.) Schweiz. Ztschr. f. Path. u. Bakt. 10 [Suppl.]: 109-124, 1947.—The authors present clinical and pathologic findings in 4 cases of giant follicular lymphoblastoma, a disease about which they say they know little. They agree with the classification given by the Americans (Bachr, Klempner, and Foot) and believe it is a neoplasm occupying a place mid-way between benign and malignant tumors.—*Auth. Summ.*
- Scott, R. Bodley: Treatment of the primary lymphadenopathies. In: Discussion: Treatment of the lymphadenopathies. Proc. Roy. Soc. Med. 40: 617-621; 621-622, Sept., 1947.
- Sessa, Francesco [Univ. Catania]: Contributo alla genesi dei plasmocitomi extramidollari (plasmocitoma della guancia). [Genesis of extramedullary plasmocytoma (plasmocytoma of the cheek). Arch. per le sc. med. [Ital.] 84: 216-228, Oct., 1947.
- Sparling, H. J., Jr.; Adams R. D., & Parker, F., Jr. [Boston City Hosp. & Harvard M. Sch., Boston, Mass.]: Involvement of the nervous system by malignant lymphoma. Medicine 26: 285-332, Sept., 1947.—A histogenetic classification according to cell type is presented, based on the material available at the Mallory Institute of

Pathology: of 118 cases of malignant lymphoma autopsied, brain and spinal-cord examinations had been made in 52, most of which had had neurologic symptoms. The various types of presenting symptoms and lesions are discussed and illustrated by case reports. The authors suggest that lymphomas derived from lymphocytes, lymphoblasts and plasma cells should not arise within the brain or any structure underneath the dura, for lymphoid tissue is not a normal constituent of the brain and spinal cord. Since histiocytes are, tumors arising from them should be expected here, i.e., Hodgkin's and reticulum-cell sarcoma. 4 clinical syndromes are produced by lymphomatous disease of the nervous system: most often, acute or subacute cord compression; (2) successive implication of cranial nerves or, rarely, the cerebral cortex; (3) meningeal invasion with or without cranial or spinal nerve, or cortical invasion; (4) signs and symptoms of primary cerebral disease. Therapy entails, for the most part, surgical removal of tumor tissue causing immediate symptoms when feasible, followed by x-ray therapy. In Hodgkin's and reticulum-cell sarcoma of the brain, craniotomy followed by x-ray therapy; in Hodgkin's and reticulum-cell sarcoma, x-ray therapy is suggested.—*H. D. Diamond, M.D.*

Webster, Jolin Joseph [New York, N. Y.]: Urethane in leukemia. *J. A. M. A.* 135: 901-903, Dec. 6, 1947.—Case of chronic myeloid leukemia was treated with 3 gm. of urethane daily for 40 days; death ensued 14 days later from agranulocytosis. Selective inhibition of early myeloid cells was noted after 11 days of medication. This case is the fourth reported with deleterious effects due to urethane medication; it is the second death. The literature is reviewed.—*D. A. S.*

Wilkinson, Jolin F., & Fletcher, Frank [Univ. & Roy. Infirmary, Manchester, Eng.]: Effect of β -chloroethylamine hydrochlorides in leukaemia, Hodgkin's disease, and polycythaemia vera. Report on eighteen cases. *Lancet* 2: 540-545, Oct. 11, 1947.—The nitrogen mustards, methyl-bis and tris (β -chloroethyl) amine hydrochloride, were employed therapeutically in 18 proved and previously untreated cases: 8, chronic myeloid leukemia; 3, chronic lymphatic leukemia; 4, Hodgkin's disease; 3, polycythemia vera. The reactive portion of these chemotherapeutic agents are the nucleotoxic and cytotoxic cyclic ethylene-imonium derivatives formed when nitrogen mustards are dissolved in water; they especially affect mitosis in more rapidly proliferating cells, and enzyme systems—hence the hematopoietic and gastrointestinal systems particularly. The tris form was preferred since it caused less venous thrombosis at the site of injection. 3 to 6 doses were given, daily or on alternate days, of 0.1 to 0.2 mg./Kg. of body wt.; the calculated dose was freshly dissolved in 30 ml. of sterile isotonic saline and given intravenously without delay. Careful daily peripheral hematologic and interval sternal-marrow studies were done before, during, and after treatment. Toxic effects were pain and thrombosis at the local injection site, nausea,

vomiting, anorexia, diarrhea, headache and vertigo; delayed phenomena were leukopenia, granulopenia, thrombopenia, and even severe anemia associated with bone-marrow aplasia. Subjective improvement, manifested by disappearance of fever and constitutional symptoms, objective decrease in lymph node and spleen size, and fall in abnormally high white blood-cell levels, sometimes even with rise in hemoglobin, were seen. The best effects were obtained in chronic myeloid leukemia and Hodgkin's disease; only moderate results, in chronic lymphatic leukemia; and the least effects, in polycythemia vera. Response to treatment appears to diminish after repeated injections. The nitrogen mustards are palliative agents only, not curatives. They do cause remissions in the mentioned maladies, but these remissions are rarely maintained.—*H. D. Diamond, M. D.*

Winer, L. H. [Beverly Hills, Calif.]: Mycosis fungoides. Benign and malignant reticulum cell dysplasia. *Arch. Dermat. & Syph.* 56: 480-498, Oct., 1947.

Wintrobe, Maxwell M.; Huguley, Charles M., Jr.; McLennan, Margaret T., & Carvalho, Lucio Penna de [Univ. Utah Sch. Med., Salt Lake City, Utah]: Nitrogen mustard as a therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. *Ann. Int. Med.* 27: 529-540, Oct., 1947.—Nitrogen mustard as methyl-bis β -chloroethylamine, $\text{CH}_3\text{N}(\text{C}_2\text{H}_4\text{Cl})_2$, commonly called HN_2 , was used. The usual dose was 0.1 mg./Kg. of body weight given in 4 to 6 daily saline infusions. The largest dose used was 0.25 mg./Kg. Maintenance therapy at 2- to 4-wk. intervals was given in selected instances. The drug was noted to be a hematopoietic toxin and a gastrointestinal irritant. Only one case of phlebotrombosis was recorded. Reactivity to nitrogen mustards is so great that blood-vessel occlusion to a given area for 5 minutes protects that area from the effects of the drug. 77 patients were treated: 65 with Hodgkin's disease, lymphosarcoma, or chronic myelogenous, lymphatic, or acute leukemia; and 12 with other neoplasms (2 presumptive Hodgkin's disease, 4 metastatic carcinomas, 2 multiple myelomas, 1 malignant melanoma, 1 bronchial carcinoma, 1 Kaposi's sarcoma, 1 metastatic fibrosarcoma). Criteria of results were: if the patient was able to return to his usual occupation for several months free of troublesome symptoms, the effect was labeled, "good"; definite improvement, more short-lived, and less striking (including cases in which a singularly harassing symptom was relieved), "fair"; those that showed little or no improvement, or remission was of very short duration, "poor." Results were: 28 cases of Hodgkin's disease—61% good, 18% fair, 21% poor, 15 living 1 to 26 mos. since first treatment; 11, lymphosarcoma—36% good, 64% poor, 2 living 2 to 5 mos. after treatment; 8, chronic myelogenous leukemia—43% good, 14% fair, 43% poor, 6 alive 1 to 22 mos. after treatment; 10, chronic lymphatic leukemia—30% good, 10% fair, 60% poor, 6 alive 1 to 24 mos. after treatment; 8,

acute leukemia—38% fair, 62% poor, none living.

In Hodgkin's disease the striking effect was the quickly broken fever. Increase in appetite, well-being, and weight gain also occurred. Remissions lasted from 3 wks. to 27 mos. Lymph nodes and spleen decreased in size, and in some cases with mediastinal and parenchymal disease, cough, dysphagia, and dyspnea were relieved. 5 so-called x-ray resistant cases improved markedly. Because of its ease of administration nitrogen mustard sometimes has an advantage over x-ray therapy in Hodgkin's disease and leukemia. In lymphosarcoma, the effect was unpredictable, ranging from dramatic to nil. No response in the x-ray resistant patients was noted. When a favorable response occurred in chronic myelogenous leukemia, the white cell and platelet counts approached normal limits, and anemia was allayed. The spleen became smaller, and weight was gained. In chronic lymphatic leukemia, that group whose blood findings were unaccompanied by other signs or symptoms were responsive to nitrogen mustard; whereas, the cases of long standing, with marked lymphadenopathy, splenomegaly, thrombocytopenia, and severe anemia were refractive. In 2 cases of acute leukemia the drug was ineffective except for relief of acute bone pain.—*H. D. Diamond, M.D.*

Wright, Angus [Los Angeles, Calif.]: California Cancer Commission Studies. Chapter VIII. Malignant lymphoma. California Mcd. 67: 386-389, Dec., 1947.

MUSCULOCUTANEOUS SYSTEM

Budd, John [Los Angeles, Calif.]: California Cancer Commission Studies. Chapter VI. Sarcoma of soft tissues. California Mcd. 67: 249-251, Oct., 1947.—Review.

Clement, Kenneth W. [City Hosp., Cleveland, O.]: Fibromyxoma of the right thigh and mixed dermoid and serous cyst of the right ovary: report of a case. J. Nat. M. A. 39: 261-262, 273, Nov., 1947.

Geyer, A.: À propos d'un histiocytosarcome, à évolution mortelle, observé en A. O. F. [A histiocytic sarcoma with fatal outcome, seen in French West Africa]: Rev. méd. nav. 2, [3]: 205-213, 1947.

Khanolkar, V. R. [Tata Mem. Hosp., Bombay, Ind.]: Granular cell myoblastoma. Am. J. Path. 23: 721-739, Sept., 1947.—Six case reports.

Oosthuizen, S. F. & Barnetson, James [Univ. Pretoria and Inst. Siektekunde, Pretoria, S. Africa]: Two cases of lipomatosis involving bone. Brit. J. Radiol. 20: 426-432, Oct., 1947. Two adult male patients, 1 a European and 1 a native, were treated for enormous enlargement of the right foot—a lipomatosis causing expansion and destruction of bone and of joints. Muscle and other soft tissues were also involved in at least 1 of the cases. This lipomatosis began

very early in life and remains confined to the affected area although involving the tissues diffusely in that area. The radiological and pathological appearances are described. In the literature at present available to us, no description of a similar condition could be found.—*Auth. Summ.*

Tesler, James & Koiransky, Henry [Cumberland Hosp., Brooklyn, N. Y.]: Liposarcoma of the capsule of the left kidney complicating nephrolithiasis and pyonephrosis. Case report with autopsy. Am. J. Roentgenol. 58: 641-643, Nov., 1947.

SKIN

Bloom, David, & Ginzler, Arthur M. [Sydenham Hosp., and N. Y. Post-Grad. M. Sch. and Hosp., New York, N. Y.]: Myoblastoma. Report of a case of myoblastoma of the lip followed by multiple tumors of the skin. Arch. Dermat. and Syph. 56: 648-658, Nov., 1947.—The authors emphasize 2 features: the squamous-cell epithelioma-like changes in the overlying epithelium of the lip and the multiplicity of the lesions.—*M. C. J.*

Cipollaro, Anthony C. [N. Y. M. Coll. and Flower Fifth Avc. Hosps., New York, N. Y.]: Cancer of the skin. Pennsylvania M. J. 51: 180-187, Nov., 1947.

Clifton, F., & Gordon, W. H. [London]: A case of an adenoma arising in a sweat gland of the upper eyelid. Brit. J. Ophth. 31: 697-700, Nov., 1947.

Daland, Ernest M. [Mass. Gen., Pondville, and Palmer Mem. Hosps.; Harvard M. Sch., Boston, Mass.]: Radical treatment of malignant melanomas of the lower extremities. S. Clin. North America 27: 1136-1143, Oct., 1947.—Report of 3 cases.

Eberhard, Theodore P. [Jefferson M. Coll. and Hosp., Philadelphia, Pa.]: Treatment of epitheliomas of the skin. Radiology 49: 620-626, Nov., 1947.

Glover, D. M. [Cleveland, Ohio]: Surgical treatment of irradiation dermatitis and carcinoma. Am. J. Surg. 74: 735-746, Nov., 1947.—The various types of skin injury following roentgen ray or radium treatment for a variety of conditions are reported. The resulting unfortunate sequelae range from acute burns to malignancy. Illustrative case reports are given, together with the pathologic findings and the plastic repair. Worthy of note are the long interval between the original treatment and the development of malignant change as well as the types of carcinoma found at operation. A report of the unfavorable results of irradiation which inevitably come to the attention of the plastic surgeon should not discourage the use of this powerful agency under proper conditions and for proper indications. It is suggested, however, that its use in the treatment of benign conditions which can be handled effectively by other means might be curtailed.—*Auth. Summ.*

- Gordon, Hugh W. [Eng.]: Pringle's disease (adenoma sebaceum). *Proc. Roy. Soc. Med.* 40: 700, Oct., 1947.
- Halpern, Lawrence K. [Barnard Free Skin & Cancer Hosp. & Washington Univ. Sch. Med., St. Louis, Mo.]: Development of squamous cell epithelioma in epidermolysis bullosa. Report of a case. *Arch. Dermat. & Syph.* 56: 517-522, Oct., 1947.
- Masson, Pierre [Montreal, Quebec]: Névrome myélinisé dermique associé à un naevus bleu. [Dermal myelinated neuroma associated with blue nevus.] *Schweiz. med. Wchnschr.* 77: 1154-1155, Nov. 1, 1947.—Case report.
- O'Leary, Paul A., & Montgomery, Hamilton [Mayo Clin., Rochester, Minn.]: Xanthomatosis. *Canadian M. A. J.* 57: 445-452, Nov., 1947.
- Osborne, Earl D.; Jordon, James W.; Hoak, Frank C., & Pschierer, Francis J. [Univ. Buffalo Sch. Med., Buffalo, N. Y.]: Nitrogen mustard therapy in cutaneous blastomatous disease. *J.A.M.A.* 135: 1123-1128, Dec. 27, 1947.—The history, origin, pharmacology, and toxicology of the nitrogen mustards are reviewed. 2 cases of mycosis fungoides, 1 of lymphosarcoma, 1 of Kaposi's hemorrhagic sarcoma associated with Hodgkin's disease, and 1 of chronic disseminated lupus erythematosus were treated with the methyl-bis form: 0.1 mg./Kg. body weight in 5.0 cc. normal saline for 4 doses ($\frac{3}{4}$ dose given in lupus). Rapid good remission occurred in the mycoses but symptoms recurred in one; the other received two series, the 2d apparently without effect. Early relief of itching was dramatic. The lymphosarcoma showed excellent tumor regression, but death from pneumonia occurred 12 days after start of treatment: no gross or microscopic evidence of lymphosarcoma was found in lymph nodes, viscera or skin at autopsy. There was no effect in the Kaposi's sarcoma. The case of lupus had a 3-mo. remission; the drug is not advocated in lupus, however, because of its inflammatory nature.—*H. D. Diamond, M.D.*
- Pack, George T. [Mem. Hosp., New York, N. Y.]: The management of pigmented nevi and malignant melanomas. *South. M. J.* 40: 832-838, Oct., 1947.—Malignant melanoma is the most malignant and dangerous of all accessible cancers, yet a great majority are preventable by early and appropriate treatment of the common pigmented mole. Pigmented nevi and melanoma are not commonly found in the darker races. When found in the Negro, they occur most often in such locations as the sole of the foot, the nail bed, and the oral mucosa. There is a type of pigmented nevus that bears such a close resemblance to melanoma that it is not possible to differentiate them clinically. These occur in children up to the time of puberty. In the author's experience of more than 900 cases of malignant melanomas, none of the melanotic tumors of childhood has metastasized to regional lymph nodes. The author recommends the term "pre-pubertal melanoma" for this group. The treatment of pigmented nevi and malignant melanomas is surgical excision. X-ray therapy and radium are of no avail, since these tumors are notoriously radio-resistant. The ideal treatment for malignant melanoma is so-called excision and dissection in continuity for primary and metastatic melanoma in regional lymph nodes. When the primary occurs in the distal part of an extremity with metastatic nodes in the groin or axilla, this is not practical because of the extent of the intervening skin; interscapulothoracic amputation, or thigh disarticulation with groin dissection is recommended for these situations. The 5-yr. survival rate for operable malignant melanomas without node metastasis is 18%: with node metastases, 15%.—*A. G. James, M.D.*
- Sachs, Wilbert; MacKec, George Miller; Schwartz, Oscar D., & Pierson, Herbert S. [N. Y. Post-Grad. M. Sch. & Hosp.]: Junction nevus—nevocarcinoma. (The so-called melanoma group). *J.A.M.A.* 135: 216-218, Sept. 27, 1947.—The term "melanoma" is used too loosely, referring both to a type of nevus and a malignant growth. Junction nevus and nevocarcinoma are preferred. Nevocarcinoma is divided into early and late forms by the degree of malignancy. Junction nevus is usually a pea-sized, flat or slightly raised, smooth, nonhairy lesion of deep brown or black color. Biopsy is indicated, since the histologic picture is definite. If small, the lesion should be excised; if large, a section studied before a disfiguring operation is done. Surgical biopsy is considered a safe procedure. Important microscopically is the presence of nests of nevus cells at the junction of the epidermis and the cutis. Malignant change in a junction nevus results in nevocarcinoma, in early cases distinguished histologically by the presence of embryonic or anaplastic cells, usually with mitotic figures. In late nevocarcinoma practically all the cells are anaplastic, with variation of size and shape, granular cytoplasm and enlarged nuclei. There may be no clinical indication of these changes and they may occur with or without trauma. In treating pigmented nevi an exact diagnosis is essential. Junction nevi are to be distinguished from epidermic pigmented nevi, nevus pigmentosus and pilosus and the blue nevus (Jadassohn-Tieche). Junction nevus should be considered precancerous and treated by simple excision. Early nevocarcinoma often may be cured by wide excision. Surgery and radiation should be tried on the later forms, but the prognosis is grave.—*M. W. Stearns, M.D.*
- Saint, C. F. M. [Univ. Cape Town, S. Africa]: A clinical atlas. IV. Skin cancer. 2. Basal-celled carcinoma. *Clin. Proc.* 6: 281-285, Sept., 1947.
- Traenkle, Herbert L. [Roswell Park Mem. Inst., Buffalo, N. Y.]: Problems encountered in the treatment of cutaneous cancer. *New York State Med.* 47: 2414-2419, Nov. 15, 1947.

Tranb, Eugene F. [New York, N. Y.]: The pigmented, hairy and warty nevi and their relationship to malignancy. *South. M. J.* 40: 1000-1005, Dec., 1947.

Upshaw, Bette Young; Ghornley, Ralph K., & Montgomery, Hamilton [Mayo Clin., Rochester, Minn.]: Extensive blue nevus of Jadassohn-Tièche. Report of case. *Surgery* 22: 761-765, Nov., 1947.

NERVOUS SYSTEM

Adson, Alfred W. [Mayo Clin., Rochester, Minn.]: Brain tumors: value of early diagnosis. *Journal-Lancet* 67: 427-430, Dec., 1947.

Appelbaum, Emanuel; Norman, Jane W.; & Brenner, Joel J. [Bellevue Hosp. & Health Dept., New York, N. Y.]: Brain tumor simulating purulent meningitis. *New York State J. Med.* 47: 2106-2108, Oct. 1, 1947.

Brown, Howard A. [Univ. Calif. M. Sch., San Francisco, Calif.]: A dermoid tumor of the lateral ventricle associated with internal hydrocephalus. *J. Neurosurg.* 4: 472-476, Sept., 1947. Case report.

Buey, Paul C., & Ritehey, Hardin [Univ. Ill. Coll. Med. and Chicago Mem. Hosp., Chicago, Ill.]: Klippel-Feil's syndrome associated with compression of the spinal cord by an extradural hemangiolioma. *J. Neurosurg.* 4: 476-481, Sept., 1947. Case report.

Cross, Glen O. [M.C., A.U.S.]: Subarachnoid cervical angioma with cutaneous hemangioma of a corresponding metamere. Report of a case and review of the literature. *Arch. Neurol. & Psychiat.* 58: 359-366, Sept., 1947.

DeAngelis, C. Eugene [M.C., A.U.S.], & DeAngelis, Elizabeth Sammis [Washington, D.C.]: A large calcified intracranial oligodendroglioma. *South M. J.* 40: 838-840, Oct., 1947.—Case report.

Fattovich, Giovanni [Osp. Psichiat. Prov. Venezia]: Sclerosi tuberosa e tumore cerebrale. Studio istopatologico di due casi di glioma associati a sclerosi tuberosa. [Tuberous sclerosis and cerebral tumors. Histopathological study of two cases of glioma associated with tuberous sclerosis.] *Rassegna di studi psichiat.* 36: 424-443, July-Sept., 1947.—Description of 2 typical cases of tubercous sclerosis of Bourneville; one was associated with an extensive gliomatous tumor (neurospongioblastoma) in the striothalamic region; in the other there was a zone with blastomatous structure (spongioblastoma) in the white matter below, in connection with the cortical tuberous mass.—*Auth. Summ.*

Grant, Francis C. [Univ. & Postgrad. Hosps., Univ. Penna. Sch. Med., Philadelphia]: Intracranial meningiomas, surgical results. *Surg., Gynec. & Obst.* 85: 419-431, Oct. 1947.—Eleven years' experience with intracranial meningiomas seen in the Neurosurgical Clinics is reviewed: 149

cases, 14.8% of all (1001) brain tumors seen. Group I, tumors related to the basal structures of the brain, comprised 64 cases: 13 bilateral frontal, 17 sphenoid ridge, 13 frontotemporal, 7 suprasellar, 3 gasserian ganglion, and 11 cerebellar tumors. 31 of these were removed completely and 32 partially, with 16 deaths (case mortality, 25%). Group II, tumors lying over the brain convexities, comprised 82 cases: 37 frontal, 9 frontoparietal, 10 temporal, 11 parietal, 12 parieto-occipital, and 3 interventricular tumors. 64 of these were removed completely and 18 partially, with 9 deaths (case mortality about 10%). Apparently the more closely the tumor lay to the carotid vessels, olfactory groove, suprasellar area, sphenoid ridge, and to the base of the skull, gasserian ganglion and posterior fossa, the higher the mortality and the less the chance of a complete removal. 3 cases verified as meningioma at autopsy in which no operation was performed are not included in either group. There were 25 operative and 3 nonoperative deaths in the entire series. 113 of the 129 survivors were followed successfully: 11 have died since 1935, 7 from recurrent tumor and 4 from intercurrent disease. Of the remaining 102, 34 are alive, well and working, and in as good physical condition as prior to operation; in 31 the tumors were completely removed, hence can be considered cured, (20% of total relieved of all symptoms); the 3 in which the tumors were partially removed may be expected to present recurrences, with return of symptoms. 68 others survived but are handicapped by postoperative complications: 17, loss of vision, present in each case prior to operation; 31, postoperative convulsive attacks (noted in 21 preoperatively, in 10 developed as a result of the operation); 20 have either a complete or partial hemiparesis or spasticity in the contralateral extremities (13 live reasonably useful lives, 7 are badly incapacitated). 163 operations were performed on the 149 cases, with 25 deaths. 7 were operated upon in two stages; 4, twice and 3, three times, for recurrence. The overall mortality was 15.5%. In 33, localization of the lesion was obtained by ventriculography but was impossible by careful neurological studies and routine x-ray examinations. No air studies were made in another case. In the remaining 115, the location was obvious either from neurological examination, including study of the visual fields, or from the flat x-ray plate. Flat x-ray films were entirely negative in 48; in 81 they strongly suggested the position, and in 38 of these not only was the position of the lesion correctly estimated but a positive diagnosis of meningioma was reached. In 10, the x-ray reports were entirely misleading as to position. Ventriculograms were performed in 61 cases with 2 missed diagnoses, both because of insufficient air. In 20, an encephalogram was made, localizing the tumor accurately in 16 with 4 failures.

Strict attention is paid to the preoperative and postoperative serum protein levels, and Amigen and whole blood are used liberally. All cranial tumor surgery is carried out with the patient horizontal (the erect, or sitting, position

- is used only in trigeminal root sections). Local anesthesia, plus morphine, is the choice in craniotomy for a supratentorial tumor. Endotracheal ether is used in all suboccipital craniotomies, with the patient in the prone position. Careful hemostasis during the approach to the meningioma is considered essential. The use of preoperative ventricular tap for relief of pressure and the reduction of bleeding is considered of great importance. Much time is saved by motor driven tools. The author concludes that by proper methods, diagnosis and localization of the tumor can be correctly made in 98% of cases. Electrosurgical aids, suction and especially preoperative and postoperative supportive measures, plus prompt and adequate control of intracranial pressure, have reduced the operative mortality from 21 to 8.6% in the years Jan. 1, 1946 to Dec. 31, 1946. Inasmuch as the tumors are benign, the goal is total extirpation, with minimal damage to adjacent brain areas. The operative mortality might have been improved if a more conservative attack, as represented by a two-stage procedure, had been used more often.—*J. A. Chamberlin, M.D.*
- Groszberg, Desiderius, & Blumenthal, Irving J. [Vet. Adm. Hosps., Northport, N. Y. & Bedford, Mass.]: Subcortical fibroblastoma of the brain. A case report. *Am. J. Path.* 23: 741-753, Sept., 1947.
- Howie, Tom O. [Victoria Infirmary, Glasgow]: The significance of vertigo and nystagmus in cases of brain tumour. *M. Press* 218: 256-260, Sept. 17, 1947.
- Koella, Werner [Univ. Zürich, Swt.]: Das Angiogliom. [Angioglioma] *Schwiz. Arch. f. Neurol. u. Psychiat.* 59[1/2]: 208-238, 1947. Review of the literature and 6 case reports: 4 tumors unquestionably angiogliomas, 2 equivocal.
- Larson, Lawrence M. [Minneapolis, Minn.]: Lumbar retroperitoneal ganglioneuroma. Review of literature and report of case. *Minnesota Med.* 30: 969-971; 977, Sept., 1947.
- Morris, Arthur A. [Baptist Mem. Hosp., Memphis, Tenn.]: The use of the smear technique in the rapid histological diagnosis of tumors of the central nervous system. Description of a new staining method. *J. Neurosurg.* 4: 497-504, Nov., 1947.—A rapid method of diagnosing cerebral tumors using smears of tissue fragments obtained at operation and stained with eosin and methylene blue is described. A tissue fragment is smeared on a glass slide, dried, and stained immediately: Stain with eosin 5-10 sec.; wash in water; dehydrate with acetone-alcohol; wash in water; stain with methylene blue 10-30 sec.; wash in tap water; dehydrate with acetone-alcohol; dehydrate with chloroform; clear in toluol; mount. The author used this method in the presumptive diagnosis of 116 tumors of the central nervous system. Less than 1 minute is required for the complete preparation. Nuclei stain blue, cytoplasm gray to pink, collagen brilliant pink, glial fibers pink, and intracellular phagocytized particles blue. Intracytoplasmic fibrils may be seen in piloid astrocytomas. "Gitter" cells can be distinguished from tumor cells of the same size by the meshlike cytoplasm in the former. Mucicarmine and glycogen stains are particularly successful. Sections can be kept for at least 3 years. The method is rapid, simple, reveals more mitotic figures than the usual frozen or fixed section, and the results, histologically, are comparable to these of the routine hematoxylin and eosin staining. Ten photomicrographs are shown including those of an ependymoblastoma, medulloblastoma, bipolar spongioblastoma, meningioma, glioblastoma multiforme, normal brain, and a hemorrhagic brain cyst.—*P. J. Fitzgerald, M.D.*
- Mossberger, Joseph I. [Univ. Colo. Sch. Med. & Hosps., Denver, Colo.]: Perforated duodenal ulcer and neoplasm of the tuber cinereum in the newborn. *J. Neuropath. & Exper. Neurol.* 6: 391-400, Oct., 1947.—Case report—hamartoma.
- Ray, Bronson S. [Cornell Univ. M. Coll., New York, N. Y.]: Recent advances in neurosurgery. *New York Med.* 3: 19-22; 40-42, Oct. 5, 1947.
- Reale, Guido [Univ. Siena, Italy]: Contributo allo studio dei tumori intra ed extracerebellari. [Contribution to the study of intra- and extracerebellar tumors.] *Rassegna di studi psichiat.* 36: 488-517, July-Sept., 1947.—Includes polymorphous-cell glioblastoma; telangiectatic glioblastoma; neoplastic pseudocyst of the right cerebropontine angle.—*M. C. J.*
- Silva, J. A. Caetano da, Jr., & Tenuto, Rolando [Fac. Med. Univ. Sao Paulo, Brasil]: Astrocytoma da região frontoparietal. [Astrocytoma of the frontoparietal region.] *Arq. de neuropsiquiat.* [Sao Paulo]: 5: 295-298, Sept., 1947.—Case report.
- Strong, Richard M. [Vet. Adm. Hosp., Kansas City, Mo.]: Primary melanoblastoma of the cerebellar leptomeninges with widespread extracranial metastases. Report of a case. *Arch. Path.* 44: 477-484, Nov., 1947.
- Sweet, William H. [Mass. Gen. Hosp.; Harvard M. Sch.; & Cushing Vet. Hosp., Boston, Mass.]: Relief of pain by operations on the central nervous system. *S. Clin. North America* 27: 1254-1262, Oct., 1947.
- White, James C. [Mass. Gen. Hosp. & Harvard M. Sch., Boston, Mass.]: Procaine block of the sympathetic nerves in the study of intractable pain and circulatory disorders. *S. Clin. North America* 27: 1263-1280, Oct., 1947.

EYE AND EAR

- Esterman, Benjamin; Laval, Joseph, & Okrainetz, Clara [Manhattan Eye, Ear & Throat Hosp., New York, N. Y.]: Intraepithelial epithelioma of the cornea and conjunctiva

- (Bowen's disease). *Am. J. Ophth.* 30: 1537-1540, Dec., 1947.—Case report.
- François Jules [Charleroi]: Schwannome intra-oculaire. [Intraocular schwannoma.] *Ann. d'ocul.* 106: 542-546, Sept., 1947.—Schwannoma of the uvea in a 44-yr.-old woman with latent von Recklinghausen's syndrome as shown by café au lait spots along peripheral nerves.—*M. C. J.*
- Grossman, Arnold A.; Donnelly, W. Allen, & Snitman, Maurice F. [Univ. Ill. Coll. Med., Chicago, Ill.]: Carcinoma of the middle ear and mastoid process. *Ann. Otol., Rhin. & Laryng.* 56: 709-721, Sept., 1947.—Case report.
- Halpert, Béla, & Patzer, Reynold [Sch. Med. Univ. Okla., Oklahoma City, Okla.]: Maxillary tumor of retinal anlage. *Surgery* 22: 837-841, Nov., 1947.—The clinical history is presented of a 6-month-old white girl who had a tumor removed from the maxilla. The neoplasm, composed of tissue elements of the retina, is believed to be the first tumor of retinal anlage ever recorded.—*Auth. Summ.*
- Javett, S. N., & Samuel, Eric [Johannesburg, S. Africa]: Tumor of the optic chiasma. *Arch. Dis. Childhood* 22: 248-250; 259, Dec. 1947.—Case report.
- Kilgour, J. M., & Cameron, Hugh [Winnipeg Gen. Hosp., Canada]: A case of acoustic nerve neuroma. *Manitoba M. Rev.* 27: 583, Oct., 1947.
- Less, V. T. [Blackpool, Eng.]: A case of metastatic osteosarcoma in the choroid. *Brit. J. Ophth.* 31: 713-716, Dec., 1947.—Case report.
- Myer, Bernard C. [Mt. Sinai Hosp., New York, N. Y.]: Some observations on tumor of the acoustic nerve. *New York State J. Med.* 47: 2436-2438, Nov. 15, 1947.
- Unger, Kuno [Haifa, Palestine]: Neurofibromatosis iridis (Recklinghausen's disease). *Arch. Ophth.* 38: 655-659, Nov., 1947.—Two case reports.
- Berner, A. [L'Hôpital cantonal d'Aarau]: Un cas de plasmocytome primitivement solitaire avec hyperglobulinémie β_2 . [Case of single, primary plasmocytoma with β_2 hyperglobulinemia.] *Schweiz. med. Wchnschr.* 77: 1104-1106, Oct. 18, 1947.—Tumor in the body of the 1st lumbar vertebra with spontaneous fracture.
- Bogart, Franklin B., & Imler, Allison E. [M. C., A. U. S., Letterman Gen. Hosp., San Francisco, Calif.]: Fibrous dysplasia of bone. *Am. J. Roentgenol.* 58: 478-485, Oct., 1947.—Discussion and report of 4 cases.
- Bogart, Franklin B., & Imler, Allison E. [M. C., A. U. S. Inactive]: Giant-cell tumors of bone. *Radiology* 49: 432-440, Oct., 1947.
- Brailsford, James F. [Roy. Cripples, & Queen Elizabeth Hosps., Birmingham, Eng.]: Some experiences with bone tumours. (*Abridged*). *Proc. Roy. Soc. Med.* 40: 787-794, Nov., 1947.
- Coley, Bradley L., & Santoro, Anthony J. [Mem. Hosp., New York, N. Y.]: Benign central cartilaginous tumors of bone. *Surgery* 22: 411-423, Sept., 1947.—Twenty-two central chondromas and 8 benign chondroblastomas—"Codman's epiphyseal chondromatous giant-cell tumors"—from the Bone Tumor Department were studied. The authors agree with others that the latter are of cartilaginous origin, not giant-cell tumors. Most of the cases of chondromas or enchondromas were 10 to 30 yrs. of age; sex distribution was almost equal. Except for 1 rib only long bones of extremities were affected: more than 1/3 were of phalanges. If present, symptoms were usually trivial: pain, swelling, ecchymosis, deformity and infrequent disability; however, pathologic fractures, particularly of the phalanges, were observed. There is no satisfactory theory of etiology. Gross and microscopic findings of cartilaginous elements are usually characteristic. While the x-ray appearance of a circumscribed translucent area in the end of a long bone suggests the diagnosis, surgical exploration and complete extirpation of accessible central bone lesions affords satisfactory treatment and permits microscopic diagnosis. X-ray therapy, used in 4 cases, is considered valueless. Complications were minimal. Good anatomic, functional and economic results of 1 to 14 yrs. were obtained; exceptions were 2 cases too recent to evaluate, 3 deaths and 1 amputation. The chondroblastomas were equally divided between the sexes: 1/2 occurred in ages 11 to 20; all were in long bones, mostly femur and humerus. The authors' experience supports Jaffe and Lichtenstein that these tumors probably begin in the epiphysis and involve the metaphysis secondarily. Local pain and swelling are the usual symptoms. X-ray evidence may suggest a malignant bone sarcoma. The authors admit the possibility of satisfactory x-ray therapy, for these tumors are somewhat radiosensitive, but prefer surgery because it has proved satisfactory and usually essential to accurate diagnosis.—*S. A. Wilkins, Jr., M. D.*

OSSEOUS SYSTEM

- Amies, A. B. P.: An unusual osteoid tumour of the mandible. *Australian J. Dent.* 51: 273-275, Sept., 1947.—Case report.
- Anon. [N. Y. Inst. Clin. Oral Path., New York, N. Y.]: Giant cell tumor. *New York State Dent. J.* 13: 474-476, Oct., 1947.—Case report.
- Bandler, Herbert, & Kyrle, Paul [Chir. Univ.-klin. Vienna, Austria]: Zur Frage der malignen Umwandlung, "gutartiger" Riesenzellengeschülste. [The question of malignant transformation of "benign" giant-cell tumors.] *Wien. klin. Wchnschr.* 59: 730-732, Nov. 7, 1947.—Two cases are reported which support, although they do not prove, the contention of malignant degeneration of an initially benign tumor.
- Gergely, Lewis [Debrecen, Hungary]: Central

myxoma of the mandible. *Am. J. Orthodontics* 33: 810-814, Nov., 1947.—Case report.

Griswold, R. Arnold [Univ. Louisville Sch. Med., Louisville, Ky.]: Osteochondrosarcoma of the sternum. Use of tantalum plate as a prosthesis. *Arch. Surg.* 55: 681-688, Dec., 1947.—A case is reported in which a large portion of the anterior thoracic cage was removed because of osteochondrosarcoma of the sternum. A large tantalum plate was fitted into the defect. This plate functioned satisfactorily as a temporary prosthesis.—*Auth. Summ.*

Hankey, George T. [London Hosp., Eng.]: Three cysts in the same mandible, not of dental origin. ? solitary cysts or osteitis fibrosa. *Proc. Roy. Soc. Med.* 40: 723-726, Oct., 1947.

Jaffe, Henry L. [Hosp. Joint Dis., New York, N. Y.]: Tumors of the skeletal system: pathological aspects. *Bull. N. Y. Acad. Med.* 23: 497-511, Sept., 1947.—Certain aspects of osteoid osteoma, giant-cell tumor, osteogenic sarcoma, fibrosarcoma, chondrosarcoma, Ewing sarcoma, and multiple myeloma are discussed. Osteoid osteoma is a benign, solitary, small, painful tumor of bone, usually occurring in adolescents or young adults; about one-half the cases affect the tibia or femur. It develops as a nidus of osteoid and trabeculae of newly formed osseous tissue in vascularized osteogenic connective tissue. The lesion is quite disabling, but relief is prompt and permanent when excised. Giant-cell tumor is a distinctive, rare tumor with predilection for the ends of long bones; it occurs in patients more than 20 yrs. old. The entity has frequently been confused with other lesions. True giant-cell tumor is composed of spindle or ovoid stromal cells heavily interspersed with multinucleated giant cells, and its prognosis is generally bad because of its tendency to metastasize. The tumor is graded from I to III on the basis of the atypism of the stromal cells. Grade I shows no appreciable atypism, but Grade III is frankly malignant, and Grade II shows such aggressive tendencies locally that the affected limb has to be amputated.

Osteogenic sarcoma is the most common of these primary malignant bone tumors, occurs in the end of a long bone, and usually in the age group from 10 to 25 yrs. The mortality is high in all types of treatment and the author's 5-yr. survival rate is less than 10 per cent. The tumor is a sarcoma of connective tissue of bone that forms osteoid or osseous tissue. The lesion begins in the interior of the bone, grows through the cortex, metastasizes by the hematogenous route to the lungs, and death usually occurs within 2 years after the beginning of treatment. X-ray examination is relatively easy because of the age of the patient, and the location and striking radiopacity of the lesion. Fibrosarcoma of bone is a primary connective-tissue sarcoma that does not demonstrate any osteogenic potentialities. Its anaplastic form has a very ominous prognosis, but the more differentiated types are of lesser malignancy. X-ray examination may not disclose its early origin in the interior of bone, and, unless

soft tissue technique is used, its later extra-cortical growth may not be discovered.

Histologically, the tumor may resemble an osteogenic sarcoma where osteoid or bone tissue has not been formed. Chondrosarcoma is a malignant tumor arising from preformed cartilage—an enchondroma or the cartilage cap of an osteochondroma. It occurs most commonly in the long bones, the innominate, or the ribs in patients from 25 to 50 yrs. old. The tumor is slow growing and, if surgically excised, has a better prognosis than either osteogenic sarcoma or fibrosarcoma. Ewing sarcoma is a rare, malignant, primary bone tumor affecting patients 10 to 25 years of age. Usually there are the associated clinical findings of persistent fever, anemia, and increased sedimentation rate. A long bone, or one in the trunk is the most frequent site. Only an occasional patient survives. The tumor is derived from the cells of the supporting framework (the reticular tissue) of the bone marrow, and the histological diagnosis has to be made with circumspection. Multiple myeloma is a malignant tumor arising from the myeloid-formative tissue and may involve all bones in a patient. The disease usually progresses rapidly, but, occasionally, it may remain localized for months or years. Renal changes are pathognomonic, and amyloid disease of the tumor and non-tumor areas may occur. X-ray diagnosis may be faulty early in the disease because of overemphasis on the importance of multiple lesions or involvement of the calvarium. The predominant cell types are: small cells resembling plasma cells; and a cell larger than myeloblasts that shows abundant cytoplasm, and large, round, or oval nuclei.—*P. J. Fitzgerald, M. D.*

Lichtenstein, Louis, & Jaffe, Henry L. [Hosp. Joint Dis., New York, N. Y.]: Multiple myeloma. A survey based on thirty-five cases, eighteen of which came to autopsy. *Arch. Path.* 44: 207-246, Sept., 1947.—Multiple myeloma affects males slightly more commonly than females, is rare in those less than 30 years. More than 75% occur in those 40 to 60 yrs. of age. Pain, especially in the back or thorax, weight loss, pathological fracture, and palpable tumor in a superficial bone are the commonest initial complaints. A vertebral-column lesion, usually lumbar, is the initial lesion in more than half. Symptoms due to compression of the spinal cord or sciatic nerve occur. The long bones, especially the femur, are the second most common site. The course is usually progressive and rapid, lasting about 2 yrs. from onset although cases of 10 years' survival are recorded. The skeletal lesions are not the punched-out areas usually described, but result from diffuse replacement of marrow by tumor with erosion of spongy trabeculae and cortical bone. Bulky tumors and destruction of contiguous vertebral bodies occur. The radiographic changes may be insignificant, or the bone may appear as a honey-combed shell. The importance of calvarium lesions has been overemphasized radiographically.

An appreciable anemia occurs in more than

70% of cases; about 50% show a moderate or severe anemia. The total white count is not greatly altered. Myeloma cells may be seen in the peripheral blood. The authors report a total cell count of 40,000 in one patient and 30 to 54% were called plasma cells. Sternal-marrow aspiration is usually diagnostic. Hypercalcemia and hyperproteinemia each occurs in about half the cases and their concomitant presence is strongly suggestive of the disease. Serum phosphatase is normal. Benec-Jones proteinuria was present in 10 of the 26 cases examined. Uric acid is increased. Renal involvement may lead to renal impairment or to insufficiency. Microscopic findings were present in about one-half the kidneys. The lesion consists of proteinaceous plugs in the tubules with inflammatory and giant-cell reaction about the casts. It may occur in the absence of Benec-Jones proteinuria. About 10% of the authors' cases showed amyloidosis and in the skeleton the lesions were found in the tumor. Extraskelctally, bulky deposits of amyloid were present in muscle, joint capsules, and other unusual areas. In cases of atypical amyloidosis the diagnosis of multiple myeloma should be considered. Very few reports of solitary myeloma are convincing, although, occasionally the discovery of a single lesion is followed by survival for as long as 10 yrs. Two cell types are present: (1) frequently a small, uniform cell resembling the plasma cell predominates; (2) a large cell with abundant cytoplasm, and a large, round, oval, or even reniform stippled nucleus occurs. Admixtures of these are found as are atypical cells with large, bizarre, or giant nuclei. Treatment with radiation, radioactive phosphorus (P^{32}), stilbamidine, or pentamidine does not appear to alter the course of the disease. Surgical therapy is usually limited to the care of bone fractures and cord compression. Rarely, ablation of a limb for solitary myeloma has been followed by survival for some years.—*P. J. Fitzgerald, M.D.*

Rubinstein, Michael A. [Montefiore Hosp., New York, N. Y.]: Chemotherapy of multiple myeloma; the use of antimony. (Preliminary Report.) *Blood* 2: 555-563, Nov., 1947.—Seven cases of multiple myeloma were treated with antimony derivatives. Since previous observations have shown antimony to be a useful therapeutic agent in the treatment of diseases manifesting a hyperglobulinemia, a rationale was established for its use in multiple myeloma. 7 cases of multiple myeloma were treated with antimony derivatives: tartar emetic and neostibosan. 0.3 gm. neostibosan was given intravenously daily for a total of 15.0 gm. Tartar emetic was injected intravenously as a 1% solution—2 to 4 doses of 5.0 cc. each or 3 doses of 10 cc. each. The drug treatment when completed was followed by irradiation. The drugs decreased the percentage of myeloma cells in the differential count, altered the plasma cells morphologically so that metachromatic basophilic granules appeared in them only, exclusive of all other cells. No change in the hyperglobulinemia was noted. The case reports suggest that antimony tends to increase

the sensitivity of the disease to irradiation. These findings resemble Snapper's in treating multiple myeloma with stilbamidine, which, however, is not an antimony compound.—*H. D. Diamond, M.D.*

Sherman, Mary S. [Univ. Chicago, Dept. Surg., Chicago, Ill.]: Osteoid osteoma. Review of the literature and report of thirty cases. *J. Bone & Joint Surg.* 29: 918-930, Oct., 1947.

Stout, Arthur Purdy [Columbia Univ. & Presbyterian Hosp., New York, N. Y.]: Tumor Seminar [A] Undiagnosed tumor of astragalus. [B] Giant cell tumor of tibia. [C] Sacrococcygeal chordoma. *J. Missouri State M. A.* 44: 674-675; 675-676; 678-679, Sept., 1947.

Waltner, Jules G., & Karatay, Safa [Columbia Univ. Coll. Phys. & Surg., & Presbyterian Hosp., New York, N. Y.]: Cysts of the mastoid bone. *Arch. Otolaryng.* 46: 398-404, Sept., 1947.—Case report.

Zinneman, H. H. [Lincoln, Neb.]: Eosinophilic granuloma of bone. *Am. Practitioner* 2: 121-124, Oct., 1947.

RESPIRATORY TRACT

NASOPHARYNX AND SINUSES

Anon. [N. Y. Inst. Clin. Oral Path., New York, N. Y.]: Carcinoma of the antrum. *New York State Dent. J.* 13: 473-474, Oct., 1947. Case report. Squamous-cell carcinoma.

Davis, E. D. D. [Eng.]: The diagnosis and treatment of tumours of the nasopharynx. *Proc. Roy. Soc. Med.* 40: 707-712, Oct., 1947.

Koop, C. Everett; Jordan, H. Ernest, & Horn, Robert C. [Philadelphia, Pa.]: Neurilemmoma of the pharynx. *Surg., Gynec. & Obst.* 85: 641-645, Nov., 1947.—Report of 5 cases.

Novick, Joel N. [G. Washington Univ. Sch. Med., Wash., D. C.]: Osteoma of the frontal sinuses. *Arch. Otolaryng.* 46: 655-669, Nov., 1947.—Case report and review of the literature.

LARYNX

Blady, John V. [Philadelphia, Pa.]: The treatment of recurrences and evaluation of criteria for the selection of treatment of cancer of the larynx. *Am. J. Roentgenol.* 58: 331-341, Sept., 1947.—This paper attempts to set up criteria which can be used in selecting the proper modality in the treatment of recurrent cancer of the larynx. The recurrence rate after laryngofissure was 17% in 59 cases and the 5-yr. cure rate 80% to 85%. Unless the lesion involved the anterior commissure, no cartilage was removed. If the recurrence was superficial, radiation was selected, but if it was subglottic or infiltrative with possible cartilage involvement, laryngectomy was performed. No primary lesion which could be treated by laryngofissure was subjected to

radiation except where the patient's condition contraindicated surgery or if he rejected it. Of 10 recurrent cases following laryngofissure, 2 were treated with x-rays, both surviving 5 yrs., and 2 by total laryngectomy with one 5-yr. survival. Of 81 treated by radiation primarily 13 (23%) of the 56 intrinsic lesions and 6 (24%) in the 25 extrinsic lesions recurred. 12 received a 2d course of x-rays with four 5-yr. survivals. In the repeat course at least 3000 r \times 2 was given with only one case of subsequent chondritis. Two were treated by laryngectomy with one 5-year survival. It is interesting that the recurrences appeared 3 months to 8 years after the initial treatment.

There were 24% recurrences after total laryngectomy. These 15 were subsequently treated by x- or γ -irradiation or local surgical excision or by a combination of all three with no 5-year survivals. The author concludes that in this group extremely radical surgery should be tried as soon as the recurrence is detected. On the basis of an equal rate of recurrence and with less possibility of cure in post-laryngectomy recurrences, it is suggested that where radiation and laryngectomy might be equally effective, the former should be selected. However, the author prefers surgery in all Grade-III squamous carcinomas and in lesions that have infiltrated the local cartilages. A final table is included which gives specific treatment recommendations for primary lesions based upon criteria covering metastases, histo-pathology, extent of involvement, motility and mobility of the lesion and adjacent tissue, and general factors. [No data, however, are presented to substantiate such recommendations. The statistics represent only the author's experience in the treatment of recurrent cases. He further states that laryngofissure is chosen for the superficial cordal lesions because of the resulting 80% to 85%, 5-year salvage. He believes that radiation might be equally effective, but this is not recommended in his table.]—S. L. Perzik, M.D.

Hart, V. K. [Charlotte Eye, Ear, Nose & Throat Hosp., Charlotte, N. C.]: Some misleading manifestations of otolaryngological infections and tumors and their interrelationship. *Eye, Ear, Nose & Throat Monthly* 26: 596-605; 611, Nov., 1947.

Hassin, George B. [Univ. Ill. Coll. Med., Chicago, Ill.]: Carcinoma of muscle tissue as a cause of laryngeal paralysis. *J. Neuropath. & Exptl. Neurol.* 6: 358-368, Oct., 1947.—Case report.—Invasion of the muscle tissue by cancer cells results in a variety of changes in the muscle fibers—swelling, fragmentation, loss of striations, liquefaction, fibrillary disruption, degeneration and necrosis. No other muscle pathology exhibits such a wealth and combination of changes as are seen in a muscle invaded by a carcinoma. Changes in the muscles, and not in the nerves, may be the real cause of a paralysis. The degenerative changes exhibited by some muscle fibers are similar to such seen in progressive muscular atrophy and like the other changes are

of toxic and not mechanical origin. Cancer of muscle fibers differs from that of nerve fibers in involving the parenchyma; in nerve fibers, the cancer cells are confined to their mesodermal sheaths.—*Auth. Concl.*

Holinger, Paul H.; Andrews, Albert H., Jr.; Anison, George C., & Johnston, Kenneth C. [Univ. Ill. Coll. Med., & St. Luke's Hosp., Chicago, Ill.]: Pathology of the larynx. A photographic analysis. *Ann. Otol., Rhin. & Laryng.* 56: 583-613, Sept. 1947.—Includes photographs of cyst, polyp, papilloma, carcinoma.

Kemler, Joseph I. [Baltimore, Md.]: Bilateral thyrotomy for carcinoma of the larynx. *Laryngoscope* 57: 704-718, Nov., 1947.

New, Gordon B.; Figi, Frederick A.; Havens, Fred Z., & Erich, John B. [Mayo Clin., Rochester, Minn.]: Carcinoma of the larynx. Methods and results of treatment. *Surg., Gynec. & Obst.* 85: 623-629, Nov., 1947.—In this analysis of 568 patients with cancer of the larynx, an attempt is made to set up criteria for the selection of treatment in operable and inoperable cases. 446 (78.5%) were treated by surgery: 122 (21.5%), by irradiation. Of those treated surgically 213 (47.8%) had a laryngectomy, 184 (41.2%) thyrotomy, and 49 (11%) laryngeal suspension. Choice of surgery or irradiation was based on: (1) size, location, and extent of laryngeal growth, (2) grade of malignancy, (3) presence or absence of extralaryngeal extensions of the disease or metastasis to the cervical nodes, and (4) age and general physical condition of the patient. Suspension laryngoscopy with electrocoagulation or local excision was used in very limited non-infiltrating lesions of the cords. Thyrotomy (laryngofissure) was reserved for the low-grade nonfixating lesions of the anterior $\frac{2}{3}$ of one cord, or of the anterior halves of both cords including the anterior commissure. Laryngectomy was performed for cancers associated with fixation of the cords; for low-grade lesions extending through the thyroid cartilage or thyrohyoid membrane or to the postcricoid area; and for high-grade lesions without cord fixation involving the anterior $\frac{2}{3}$ of the cord. Irradiation was used in high- or low-grade lesions which were too extensive for surgical measures and in the senile debilitated patient.

A hospital mortality of only 0.47% was obtained in the last 428 surgical cases (2 deaths). This is attributed to the use of cervical block anesthesia, antibiotics and chemotherapy, a highly trained personnel, and the selected use of preoperative tracheotomy in those cases with an obstructed airway and in the aged and debilitated. The 5-yr. survival rate was 73.5% for all traced surgical cases: suspension laryngoscopy, 91.7% of 22 traced (24 total); thyrotomy, 83.6% of 73 (95 total); laryngectomy, 60.2% of 88 (104 total); for irradiation, 6.9% of 72 (76 total). [Since surgery was used in all operable groups, irradiation only in the inoperable, no figures for various types of treatment, based upon comparable groups of patients treated, are obtained; hence the author's statement that "no

one form of therapy is superior to all others" is misleading; the statement were better phrased "no one form of operative procedure is superior to all others."—*S. L. Pezick, M.D.*

Snehs, Oliver W. [Austin, Texas]: Tumors of the larynx. *Texas State J. Med.* 43: 393-397, Oct., 1947.

TRACHEA AND BRONCHI

Brunner, A. [Universitätsklinik Zürich, Switz.]: Ueber das Bronchialkarzinom. [Carcinoma of the bronchi.] *Schweiz. med. Wchnschr.* 77: 1064-1069, Oct. 4, 1947.—2 case reports.

Davies, J. N. P., & Trowell, H. C. [Mulago Hosp. M. Sch., East Africa]: A case of carcinoma of the bronchus in a Ganda male. *East African M. J.* 24: 337-338, Sept., 1947.

Ellman, Philip, & Whittaker, Hermon [Leatherhead Emergency Hosp., Surrey, England]: Primary carcinoma of the trachea. *Thorax* 2: 153-162, Sept., 1947.—Case report and review of literature.

Leddy, Eugene T. [Mayo Clin., Rochester, Minn.]: Roentgen therapy of bronchiogenic carcinoma. *Minnesota Med.* 30: 975-977, Sept., 1947.—Review of 448 cases.

McReynolds, George S. [Galveston, Tex.], & **Parish, Robert E.** [San Antonio, Tex.]: Adenoma of the bronchus. *Ann. Otol., Rhin. & Laryng.* 56: 766-768, Sept., 1947.—Case report.

Nager [Zurich, Switz.]: L'importance de l'endoscopie dans le diagnostic des affections des bronches et des poumons. [Importance of endoscopy in the diagnosis of diseases of the bronchi and lungs.] *Rev. méd. Suisse Rom.* 67: 604-607, Sept. 25, 1947.—A review.

Ochsner, Alton; DeBakey, Michael; & Dixon, J. Leonard [Tulane Univ. & Ochsner Clin., New Orleans, La.]: Primary cancer of the lung. *J.A.M.A.* 135: 321-327, Oct. 11, 1947.—An analysis of 412 cases of primary cancer of lung observed over a 12-yr. period shows an apparent increase in the incidence; it is now second only to cancer of the stomach in frequency; bronchogenic carcinoma probably comprises about 10% of all carcinomas. The increase was mostly in white patients; the incidence in Negroes changed little. 356 (86.4%) were men; 56 (13.6%) women. About 90% were in the 5th to 7th decades. The youngest was 12, the oldest 81 yrs. Of the 147 in whom pulmonary resection was performed, 76% were smokers; the distribution between indoor and outdoor occupations was almost equal. Most primary tumors of lung are malignant and of bronchogenic origin. There were 141 bronchogenic carcinomas, 2 fibrosarcomas, 2 lymphoblastomas, 1 melanoma and 1 neurogenic sarcoma. 87 (59%) were on the right and 60 (41%) on the left. The right and left upper and right lower lobes were involved in 11.6% of cases. The most common symptoms were cough, loss of weight, pain or discomfort

in the chest, previous respiratory infection, hemoptysis and dyspnea in about that order of frequency. Emphasis is placed on any change in a cough that may already have been present, and on previous respiratory infection after which there has been a persistency of symptoms. Significant symptoms are more likely if the tumor encroaches on the lumen of a larger bronchus or on the pleura.

Primary bronchial carcinoma should be suspected and surgical exploration done in every man more than 40 yrs. who has unexplained thoracic discomfort, a persistent cough, or hemoptysis. Roentgenographic (especially serial), bronchographic, bronchoscopic studies, and cytologic examination of the sputum or bronchial secretions are important diagnostically. Because of stasis from bronchial occlusion by tumor or interference with the blood supply in the center of a rapidly growing tumor, necrosis and infection may cause pulmonary abscess or bronchiectasis. In a man more than 40, lung abscess should always be considered of carcinomatous origin unless easily explained otherwise. Often a pulmonary abscess wall may appear irregular because of projecting tumor tissue. Tomograms are valuable here. 5 asymptomatic, unsuspected cases were found by routine roentgenograms. In 121 (82.3%) roentgenographic diagnosis was bronchogenic carcinoma. The diagnosis of pulmonary abscess in 8 cases (5.4%) was the most frequent error, but usually an abscess was present in association with the carcinoma. Bronchographic study is sometimes valuable, especially in lesions that are in the lung periphery or involve the bronchi of the upper lobe. Bronchoscopy, the most accurate diagnostic method, was done in 125 cases, with a biopsy in 74 (59.2%) and a positive diagnosis obtained in 61 (41.5%).

The increasing value of the cytologic examination of the sputum and the prognostic value of demonstrating tumor cells in pleural fluid are discussed. Aspiration biopsy was done only in inoperable cases. In 246 cases that were explored, a previous positive diagnosis was established in 164 (66%). The ideal treatment of primary lung cancers is pneumonectomy before the lesion has extended beyond the lung. This offers the only cure. Occasionally irradiation is beneficial but its use is not justifiable in early and operable lesions. The authors have had little experience with nitrogen mustard. The only criteria of inoperability are distant metastases, obvious involvement of the carina or trachea and the presence of cancer cells in the pleural fluid. Resection was frequently possible when the phrenic and recurrent laryngeal nerves were involved. Palliative resection is indicated when an abscess has developed in these cases.

Survival periods are sufficiently long to justify operation. Unusually, pneumonectomy is the procedure of choice. Simple lobectomy was done in 2 cases. 246 (59.8%) were explored; 99 (40.2%) proved to be nonresectable. 147 (59.8% of the number explored, 35.7% of the total series) were resected; 36 (24.5%) of these died in the hospital. Resection mortality before 1942 was 46.4%; 19.3% since. The relatively

high operative mortality (24.5%) is due to extensive disease and poor cardiovascular function. Chief postoperative complications were empyema (12.2%) and bronchial fistula (5.4%). Sulfonamides and penicillin have not materially influenced the morbidity. 63 (56.8%) have subsequently died; 48 (43.2%) are still alive (1 operated on 11 yrs. ago). 23.3% of the resected patients lived 5 yrs. (localized tumors 42.9% and extensive tumors 6.2%). The survival rate in lung cancer is now actually better than in gastric, the reported rate being about 8% and 5%, respectively. The authors conclude that the clinical course of bronchogenic carcinoma is slower than that of gastric.—*J. A. Chamberlin, M.D.*

Olsen, Arthur M. [Rochester, Minn.]: The diagnosis and treatment of lesions of the bronchial tree. *J. Missouri State M. A.* 44: 731-734, Oct., 1947.

Penta, Arthur Q. [Schenectady, N. Y.]: Primary carcinoma of the trachea removed by bronchoscopy procedure. *Ann. Otol., Rhin. & Laryng.* 56: 790-792, Sept., 1947.—Case report of epidermoid carcinoma grade 2.

Rigler, Leo G. & Merner, Thomas B. [Univ. Minn., Minneapolis, Minn.]: Planigraphy in the diagnosis of bronchogenic carcinoma. *Am. J. Roentgenol* 58: 267-276, Sept., 1947.

Shorvon, L. M. [North England Cancer Org.]: Carcinoma of the bronchus with especial reference to its treatment by radiotherapy. *Brit. J. Radiol.* 20: 443-449, Nov., 1947.

Smith, Morley T. [New Rochelle, N. Y.]: Adenoma of the trachea. *Arch. Otolaryng.* 46: 405-407, Sept., 1947.—Case report.

Stout, Arthur Purdy [Columbia Univ. & Presbyterian Hosp., New York, N. Y.]: Tumor Seminar. [A] Adenoma of Bronchus. [B] Bronchial epithelial hyperplasia and metaplasia with extension into alveoli simulating alveolar carcinoma. *J. Missouri State M. A.* 44: 679-680; 680, 682, Sept., 1947.

Whalen, Edward J. [Hartford, Conn.]: Lipoma of the bronchus. *Ann. Otol., Rhin. & Laryng.* 56: 811-818, Sept., 1947.—Case report.

Woolner, L. B., & McDonald, John R. [Mayo Clinic, Rochester, Minn.]: Bronchogenic carcinoma: diagnosis by microscopic examination of sputum and bronchial secretions; preliminary report. *Proc. Staff Meet., Mayo Clin.* 22: 369-381, Sept. 3, 1947.—Freshly collected sputum was spread on slides and fixed, while wet, in equal parts of alcohol and ether. Material that could not be spread immediately was collected in vials containing 95% alcohol. This material was later spread by gentle crushing between albumin coated slides. Both types of preparations were stained with hematoxylin and eosin, dehydrated, cleared and mounted. The characteristics of normal cells in sputum are described. Malignant cells are much larger than

normal cells, except in certain tumors characterized by small cells. The variation in the size of cells and particularly the variation of nuclear size and shape among similar cells are important criteria. In highly undifferentiated tumors the nucleus is bare or is surrounded by a narrow rim of cytoplasm. An exception is the squamous cell carcinoma with voluminous cytoplasm. The nuclei of malignant cells are hyperchromatic with a coarse chromatin network. Large and frequently multiple nucleoli are characteristic of malignant cells. Film study showed three groups of carcinomas: (1) anaplastic including small-cell, (2) squamous-cell and (3) adenocarcinoma. 70 cases of carcinoma of the lung diagnosed by sputum films are reported. 7 were of the upper lobe [and could not be visualized through the bronchoscope]. 14 did not have bronchoscopic examination for other reasons. 7 had undergone bronchoscopic examination with negative results. Positive bronchoscopic biopsy was obtained in 41. A false positive report was given in 1; subsequent necropsy showed multiple infarctions with hyperplasia and squamous metaplasia of bronchial epithelium.—*J. P. Wozencraft, M.D.*

LUNG AND PLEURA

Churchill, Edward D. [Harvard Univ., & Mass. Gen. Hosp., Boston, Mass.]: Malignant lymphoma of the lung and pulmonary coccidioidomycosis. A clinic on surgical lesions of the lung with consolidation. *S. Clin. North America* 27: 1113-1120, Oct., 1947.

Donaldson, J. K. [Little Rock, Ark.]: Diagnosis and treatment of disorders of lung requiring surgical resection. *J. Ark. M. Soc.* 44: 111-119, Oct., 1947.

Drouet, P.-L.; Herbeval, R., & Faivre, G.: Le problème des cancers suppurés du poumon. [The problem of suppurating cancer of the lung.] *Rev. méd. de Nancy* 72: 255-259, Aug.-Sept., 1947.—Three case reports.

Hochberg, Lew A.; Epstein, Israel G., & Pernikoff, Morris [Bushwick Hosp., Brooklyn, N. Y.]: Endothelioma (mesothelioma) of the pleura. (Presentation of a case treated surgically.) *Dis. Chest* 13: 621-626, Nov.-Dec., 1947.

Lambert, Adrian [New York, N. Y.]: The importance of early diagnosis in the surgical treatment of carcinoma of the lung. *New York State J. Med.* 47: 2688, Dec. 15, 1947.

McNamara, William L.; Sargent, William F., & Costich, K. J. [Vet. Adm. Hosp., Hines, Ill.]: Giant sarcoma of the pleura. Report of a case. *Arch. Surg.* 55: 632-636, Nov., 1947.—A case of giant primary fibrosarcoma of the pleura, presenting a clinical picture of pulmonary and cardiac embarrassment, is described. The diagnosis was established at autopsy.—*Auth. Summ.*

Penta, Arthur Q. [Ellis Hosp., Schenectady, N. Y.]: Bronchoscopy in early diagnosis of lung carcinoma. *Clin. Med.* 54: 399-401, Dec., 1947.

Reinhoff, William Francis, Jr. [Johns Hopkins Univ., Baltimore, Md.]: The present status of the surgical treatment of carcinoma of the lung. *Mississippi Doctor* 25: 121-132, Sept., 1947.

Simon, Morris A. [Jewish Gen. Hosp., Montreal, Quebec]: Diffuse primary alveolar carcinoma of the lung. So-called "alveolar cell" tumor of lung). *Am. J. Clin. Path.* 17: 783-796, Oct., 1947.—Case report.

Spat, Samuel D., & Grayzel, David M. [Brooklyn, N. Y.]: Primary lymphosarcoma of the lung (a case report and review of the literature). *Ann. Int. Med.* 27: 632-638, Oct. 1947,

TUMORS OF INFANCY AND CHILDHOOD

Anon.: Malignant tumors in children. Case Rep., Children's Mem. Hosp. [Chicago, Ill.] 6: 883-899, Sept., 1947.—Presentation of cases.

Krayenbühl, H., & Lüthy, F. [Univ. Zürich, Switz.] Das spinale Neurinom und sympathische Ganglioneurom im Kindesalter. [Spinal neurinoma and sympathoganglioneuroma in childhood.] *Schweiz. Ztschr. f. Path. u. Bakt.* 10: 51-65, 1947.—Five cases of tumors originating in the roots of the spinal cord are described. All began in the first decade of life, at which time tumors of nerve-sheaths are exceedingly rare. The tumors have been operated upon and the diagnoses verified histologically. 1 tumor is a neurofibroma, and 3 are neurinomas. The 5th case is a sympathoganglioneuroma. In this last case the question of the origin of the great amount of silver-stained fibrils usually seen in these tumors could be answered, because many of the ganglion cells, though more or less degenerated, could be observed to have sent out axis-cylinders.—*Auth. Summ.*

Meltzer, Adolph, & Bloom, Bernard [Beth Israel Hosp., Boston, Mass.]: Malignant testicular neoplasms in infancy. Report of a case with six-year survival. *New England J. Med.* 237: 513-515, Oct. 2, 1947.

Reed, Marjorie E. [Plymouth, Pa.] Lymphosarcoma. Report of case. *Arch. Pediat.* 64: 453-458, Sept., 1947.

Silver, Henry K. [Univ. Calif. M. Sch., San Francisco, Calif.] Wilms' tumor (embryoma of the kidney). *J. Pediat.* 31: 643-650, Dec., 1947.—Eighteen patients with Wilms' tumor of the kidney are presented. A nephrectomy was done in 13; and 10 are alive from 2¼ to 15 yrs. post-operatively, a survival rate of 76.9%. 2 were adults while the youngest patient was only 3 days old at the time of entry to the hospital. Hypertension occurred in 7 of the 8 patients in whom the blood pressure was recorded. No correlation was noted between age of onset, degree of hypertension, presence of hematuria, and the eventual outcome. No standard treatment was

used in the management of these patients, but all 4 patients who received preoperative irradiation plus nephrectomy and postoperative irradiation are alive. Every patient who survived had had a nephrectomy. The data available are insufficient to permit the evaluation of the merits of the transperitoneal as compared with the posterolateral approach to the kidney.—*Auth. Summ. & Concl.*

Slotkowski, Eugene L., & Borovsky, Maxwell P. [Cook County Hosp., Chicago, Ill.]: Adenoleiomyofibroma of the tongue. Report of a case in an infant. *J. Pediat.* 31: 470-473, Oct., 1947.

Ulfelder, Howard, & Quan, Stuart H. [Mass. Gen. Hosp., & Harvard M. Sch., Boston, Mass.] Sarcoma botryoides vaginae. Complete excision of the tumor in an infant by the combined abdominal and perineal approach. *S. Clin. North America* 27: 1240-1245, Oct., 1947.—Case report.

RESEARCH (GENERAL)

Anderson, Wm. [Glasgow Royal Cancer Hosp.]: Risk of contamination in experimental carcinogenesis. *Nature* 160: 338, Sept. 6, 1947.

Gessler, Albert E., & Grey, Clifford E. [Res. Labs. Interchem. Corp.]: Notes on the electron microscopy of tissue sections. Submicroscopic spherical bodies in carcinoma. *Exper. Med. & Surg.* 5: 307-318, Nov., 1947.—The presence of submicroscopic spherical bodies in tissue sections of carcinomatous tumors and in skin in the vicinity of a tumor is demonstrated by accompanying electron micrographs. While hundreds of such micrographs originating from normal, carcinomatous and some limited types of other pathological tissue, were taken and studied, these bodies could be clearly demonstrated only in the cancerous tissue. Their significance or unique relation to carcinoma is not determined. While their diameters are within the range of the sizes of viruses, no attempt is made to establish a relation between the two.—*Auth. Summ.*

Goldfeder, Anna [Cancer Res. Lab., N. Y. C. Dept. Hosps., & N. Y. Univ., New York, N. Y.]: "Is there any progress being made in the field of cancer research?" *Exper. Med. & Surg.* 5: 319-330, Nov., 1947.

Henshaw, P. S.; Riley, E. F., & Stapleton, G. E. [Clinton Labs., Oak Ridge, Tenn.]: The biological effects of pile radiations. *Radiology* 49: 349-360, Sept., 1947.—Some immediate and late biological effects of daily and single exposures of fast and slow neutrons, γ and β rays were investigated, using mice of CF₁, ABC, A, and C58 strains. Daily treatments of 0.115 to 13 n fast neutrons on CF₁ mice gave an L.D.₅₀ of about 200 n in 30 wks. with 1.15 n/day, and 250 n in 6 wks. with 13 n/day. Using a criterion of % shortening of life it appears that 0.25 n/day has the same effect as

8.6 r/day. For a single dose of fast neutrons, the L.D.₅₀ in 3 wks. was about 92 n. A single dose of 700 r at 3 r/min. gave an L.D.₅₀ in 40 wks., as did a dose of 78 n at 3 n/min.

For both periodic and single treatments of neutrons and γ rays, terminal changes were mainly generalized atrophy and mediastinal lymphomatosis. The incidence of lymphoma and ovarian tumors was somewhat increased. Terminal effects and peripheral blood changes due to slow neutrons resembled those due to fast neutrons and γ rays. Malignant skin changes and other abnormalities appeared in mice and Sprague-Dawley rats surviving sublethal doses of β rays.—*E. F. Focht. B.A.*

Lorenz, Egon; Heston, W. E.; Eschenbrenner, Allen B., & Deringer, Margaret K. [Nat. Cancer Inst., Bethesda, Md.]: Biological studies in the tolerance range. *Radiology* 49: 274-285, Sept., 1947. The effects of chronic exposure to low-dose rates of gamma radiation on inbred strains of mice (Strains A, C3H, dba and LAF₁ hybrids), guinea pigs and rabbits were studied, using radium element filtered with 0.5 mm. platinum. 8.8 r, 4.4 r, 2.2 r, 1.1 r and 0.11 r were given in an 8- or 24-hr. exposure period; these doses totaled approximately 3200 r, 1600 r, 800 r, 400 r and 40 r per yr. Mice were exposed for periods up to 2 yrs., the other species longer. All doses of gamma-rays produced some shortening in the life span, varying directly with the dosage. Guinea pigs receiving a total dose of 600 to 4400 r died acutely with evidence of thrombocytopenia and anemia. The bone marrow of mice and rabbits did not appear depressed, and no predominant lethal syndrome occurred. At the lower doses the mice showed increased weight gain as compared with the controls.

The carcinogenic effect of the radiations was outstanding. In LAF₁ mice, which have a high spontaneous incidence of leukemia, the onset of the disease was accelerated at the dose rates of 4.4 r and 8.8 r per day. The incidence of lung tumors, mammary carcinomas and sarcomas was greatly increased over the controls. The time of onset of lung tumors in Strain A mice, which shows a high incidence of spontaneous lung tumors, was accelerated. At 2 yrs. of age, ovarian tumors occurred in 70 to 100% of the mice exposed to irradiation in various experiments. Their development depended on the total dose administered and not on the dose rate or duration of exposure. Tumors also occurred in guinea pigs and rabbits; these normally show a very low incidence of spontaneous tumors. Female mice were sterilized at a total dose of 450 to 800 r, male mice required 800 to 1760 r; strain variation was considerable. There was no conclusive evidence of the production of genetic changes in these mice. The authors conclude it is of paramount importance that the permissible dose for man of 0.1 r per day be maintained. In women, because of the possibility of producing ovarian tumors, the permissible dose should probably be 0.02 r per day. If the rest of the body is properly shielded, the

permissible dose for the hands may be 1 r per day.—*D. A. Karnofsky, M. D.*

Mitchell, J. S. [Univ. Cambridge, Eng.]: Experiments on the mechanism of the biological action of fast neutrons using the summation method for lethal effects in mice. (With a section on dosimetry of fast neutrons.) *Brit. J. Radiol.* 20: 368-380, Sept., 1947.—The relative biological efficiency, on adult male mice, of fast neutrons of mean energy greater than 4 Mev from a Po-Bc source, and γ rays of Ra was investigated using small ionization chambers with graphite or carbon polystyrene walls. 1 r fast neutron radiation was taken to be the amount which produces the same energy absorption per unit volume of tissue as 1 r of γ radiation. Calculations were made of the ratio of the fractional energy absorption of neutrons per unit volume in tissue to that in the graphite chamber, so that readings in c.s.u. per cc. in the latter could be represented as r in tissue. In the first series of 24 experiments, 1000 r total body exposure of γ rays in 24 hours, or 35.4 r of neutron radiation, was given. Summations of 1/3 of one and 2/3 of the other of these in different order were tried. The second series of 38 experiments consisted of 2000 r of γ rays in 48 hours, or 47.2 r of neutrons. Half and half additions were also used. The criterion in each case was death within 20 days. Fractions of each radiation adding to a total of 1 were less effectively lethal than the whole given as one radiation, indicating a difference in the mechanism of action of the two. The relative biological effect in favor of the neutron was about 32 for the 48 hour exposures. Since this is greater than for short exposures it may indicate that the lethal effects of γ radiation on normal cells are produced in part by certain types of chromosome interchanges.—*E. F. Focht, B. A.*

Rachmilewitz, M.; Rosin, A.; Goldhaber, G., & Doljanski, L. [Hadassah Univ. Hosp., Jerusalem, Palestine]: Studies on bone marrow in vitro. IV. The effect of roentgen rays on explanted bone marrow. *Am. J. Roentgenol.* 58: 464-477, Oct., 1947.—The effects of x-rays (250-5000 r) on explanted rabbit bone marrow are: depression of mitotic activity and appearance of pathological mitoses; retrograde changes in, and appearance of abnormal, hemic cells; decrease in cellularity.—*D. A. S.*

Reimann Stanley P. [Lankenau Hosp. Res. Inst., Philadelphia, Pa.]: Significant trends in cancer research. *J.A.M.A.* 135: 87-88, Sept., 13, 1947.

Sano, Maeteld E., & Spiegel-Adolf, Mona [Temple Univ. M. Sch. & Hosp., Phila., Pa.]: Ultraspectrophotometric studies in extracts of normal and tumor tissue of human origin. *Science* 106: 346-347, Oct. 10, 1947.—An ultraspectrophotometric examination was made of various types of normal and neoplastic tissues obtained from thirty patients. The tissues were minced, suspended in saline (pH 7.2-7.4) and heated for 1/2 hr. at 65° C. to inhibit enzyme action. The specimen was then centri-

fuged, and the solution studied with a DU Beckman electric quartz spectrophotometer. Measurements were made in steps of 10 Å between 3,100 and 2,200 Å. Normal leukocytes showed a faint indication of selective absorption at 2,600 Å; normal liver and endometrium, 2,650 Å; inflammatory lymph nodes, 2,500 Å; carcinomas, 2,600 Å; lymphosarcoma and Hodgkin's gave a peak of 2,600 Å; lymphatic leukemia, 2,500 Å. One case, a medulloblastoma, was distinguished by two peaks at 2,550 and 2,700 Å. Of 3 benign tumors, 2 showed no selective absorption, 1 a low peak at 2,550 Å. It is considered that these observed differences are of interest from a diagnostic point of view.—*D. A. Karnofsky, M. D.*

Stilwell, E. Frances [Woman's M. Coll. Pa., Phila., Pa.]: Multipolar mitoses in tissue cultures. *J. Am. M. Women's A.* 2: 441, Oct., 1947.

Taylor, Alfred; Carmichael, Nell, & Norris, Theresa [Univ. Tex., & Clayton Found. Res., Austin, Tex.]: Temperature level and the growth of embryo and tumor of tumor-bearing eggs. *Proc. Soc. Exper. Biol. & Med.* 66: 165-166, Oct., 1947.

Truhaue, René: Recherches sur l'action cancérigène éventuelle du cholestérol irradié par les rayons X. [Studies of the possible carcinogenic action of cholesterol irradiated with x-rays.] *Compt. rend. Acad. sc.* 225: 544-546, Sept. 29, 1947.—Purified cholesterol was dissolved 5 gm./100 cc. purified benzene and irradiated with 100,000 r for 22 min. The benzene was then evaporated under reduced pressure under nitrogen and the residue suspended in sterilized neutralized olive oil, 20 gm./100 cc. 20 mice, 4 mos. old, were injected with 1 cc. of this suspension. In this group 1 lymphosarcoma developed 75 days later (characterized by the author as a spontaneous tumor). In 20 mice treated with the same type of suspension of non-irradiated cholesterol, 1 oil tumor developed, and in 20 mice injected with olive oil alone, 1 papilloma and 1 spindle-cell sarcoma were noted. The author concludes that purified cholesterol irradiated by x-rays has no carcinogenic effect.—*J. H. Burchenal, M. D.*

ANIMAL EXPERIMENTATION

Cohen, A. L.; Borsook, H., & Dubnoff, J. W. [Calif. Inst. Technol., Pasadena, Calif.]: The effect of a *Sporosarcina ureae* preparation on tumor cells in vitro. *Proc. Soc. Exper. Biol. & Med.* 66: 440-444, Nov., 1947.—The incubation of mouse spontaneous carcinoma, rabbit Brown-Pearce carcinoma, and their autologous liver slices with bacterial cultures showed in general that cells of both liver and tumor were uninjured or injured equally. Cultures of *S. ureae* damaged tumor cells and left liver cells histologically unaffected. Evidence was obtained that the selective carcinoclastic factor of *S. ureae* cultures was contained within the cells and released on autolysis.—*Auth. Summ.*

Goldfeder, Anna [Cancer Res. Lab., Dept. Hosps., & New York Univ., N. Y.]: Further studies on the relation between radiation effects, cell viability, and induced resistance to malignant growth. IV. Comparison of effects of roentgen rays on mammary tumors autogenous to inbred strains of mice (dba and C3H). *Radiology* 49: 724-732, Dec., 1947.

Greenblatt, Robert B., & Kupperman, Herbert S. [Univ. Ga. Sch. Med., Augusta, Ga.]: The relationship between sex hormones and experimentally induced tumors in rats. *Am. J. Obst. & Gynec.* 54: 584-595, Oct., 1947.—The effect of various steroid hormones upon the induction of carcinogenesis by methylcholanthrene and benzo(a)pyrene was studied. Subcutaneous and intrauterine administration of the carcinogenic agents was made by injecting either oil solutions or suspensions of the carcinogen in lard and by implantation of compressed pellets of benzo(a)pyrene. No neoplastic changes were observed in rats receiving intrauterine application of either one of the coal-tar derivatives alone or in combinations with the steroid hormones. The sarcoma-inducing effect of subcutaneously administered benzo(a)pyrene was not influenced by the simultaneously administered steroids. Transplantation of the benzo(a)pyrene-induced sarcomas appeared to be influenced by administration of hormones. Animals receiving estradiol exhibited sarcomas smaller in size than those observed in the control animals. On the other hand, progesterone, testosterone and desoxycorticosterone acetate appeared to enhance the growth of the transplanted sarcomas. Data are also presented on the effect of steroid substances on the production of neoplastic changes in the endocrine glands and accessory reproductive organs of the rat.—*Auth. Summ.*

Hartmann, Wilhelm Daniel: Die Wirkung von hohen Aussentemperaturen auf das Wachstum von 20-Methyleholanthren-Tumoren der Ratte, und die Wirkung niedriger Aussentemperaturen auf das Wachstum von 1-, 2-, 5-, 6-Dibenzanthrazen-Tumoren bei Mäusen. [The effect of high external temperatures on the growth of 20-methyl cholanthrene tumors of rats and of low external temperatures on the growth of 1-, 2-, 5-, 6-dibenzanthracene tumors in mice.] *Krebsarzt* 2: 496-500, Nov., 1947.—0.5% benzo(a)pyrene was painted on rabbit ears twice weekly; squamous-cell carcinoma ensued; rats were injected intramuscularly in the neck once weekly for 50 wks.: carcinoma and sarcoma ensued. The animals were then subjected to 41°-42°C. for 3-4 hrs. for 8 days when the tumors regressed entirely in 8 rats, 17 died of tumor cachexia, and 5 showed no effect; no effects on the rabbits. 30 rats received 0.3% 20-methylcholanthrene twice weekly with resulting sarcoma. Temperatures of 42°-43°C. for 15-37 min. were ineffective: 40-47 min., slight disappearance; 50-63 min., complete disappearance. 20 mice received 0.03% (total 3.5 mg.) on the neck twice a week for 40-54 doses. In 18-24 wks. skin carcinoma, sarcoma

of lungs, liver and kidneys developed. Temperatures of 5°-9°C. for 15-60 min. had no effect.—*M. C. J.*

Li, Min Hsin, & Gardner, W. U. [Yale Univ. Sch. Med., New Haven, Conn.]: Granulosa cell tumors in intrapancreatic ovarian grafts in castrated mice. *Science* 106: 270, Sept. 19, 1947.

Ludford, R. J., & Dmochowski, L. [Labs. Imp. Cancer Res. Fund, Mill Hill, London, Eng.]: Effect of stilboestrol on mouse tumours. *Lancet* 2: 718-720, Nov. 15, 1947.—The action of diethyl-stilbestrol has been investigated on 10 different transplantable mouse tumors including various mammary carcinomas: a carcinosarcoma, a squamous-celled carcinoma, a lung carcinoma, and 2 sarcomas in four inbred strains of mice (C57 black, Strong A, R III, and C3H). No specific inhibition of growth was found: that which occurred with relatively high dosages was the result of a non-specific toxic action. Neither in vivo nor in vitro did stilbestrol induce the same type of mitotic poisoning action as does colchicine. Genetic constitution is a significant factor in determining sensitivity to the toxic action of stilbestrol.—*Auth. Summ.*

Mann, Ida [London]: Induction of an experimental tumour of the lens. *Brit. J. Ophth.* 31: 676-685, Nov., 1947.—Neoplasms of the lens are unknown clinically, although mitoses occur in lenticular epithelium throughout life. Rabbit lenses injected with methylcholanthrene did not develop neoplasms in 10 mos. of observation. To provide a lenticular blood supply, lenses from newborn to 9-day-old homozygous mice were implanted, with methyleholanthrene, into the flank of same strain adults. After 2 to 3 mos., 26 tumors developed in 38 experiments: 3 were carcinomas of subcapsular epithelium. These grew in tissue culture, failed to grow when transplanted into mouse strains having either high or low spontaneous cancer incidence, hence are not chemically common to mice as a whole. No growth occurred on intraocular transfer to rabbits, hence they have no organ specificity.—*M. C. J.*

Parker, Raymond C.; Plummer, Helen C.; Siebenmann, Charles O., & Chapman, Marion G. [Univ. Toronto, Ont.]: Effect of histolytic infection and toxin on transplantable mouse tumors. *Proc. Soc. Exper. Biol. & Med.* 66: 461-467, Nov., 1947.

Passey, R. D.; Dmochowski, L.; Astbury, W. T., & Reed, R. [Univ. Leeds, Eng.]: Electron microscope studies of normal and malignant tissues of high- and low-breast-cancer strains of mice. *Nature* 160: 565, Oct. 25, 1947.

Silberberg, Martin, & Silberberg, Ruth [City Hosp., St. Louis, Mo.]: Hair growth in the skin of guinea pigs painted with 20-methylcholanthrene. *Arch. Path.* 44: 297-306, Sept., 1947.—In young guinea pigs benzene and, still more intensely, methyleholanthrene stimulate hair growth: Mitotic proliferation and hypertrophy

of the epithelium of the hair matrix and the hair follicle are increased, and there are indications that under the influence of the carcinogen new hair follicles and dermal papillae may be formed. This conclusion, however, should be tested in further investigations. Maximum growth is reached after approximately ½ mo. treatment. Associated with the intensification of growth are regressive changes consisting of atrophy or swelling and keratinization of hair. The matrix of the hair and the epithelium of the follicle react to these experimental stimuli more actively than the epidermis. Hair growth is more stimulated in the flank than in the ear.—*Auth. Summ.*

CHEMISTRY AND METABOLISM

Brown, George Bo-worth; Roll, Paul M., & Plentl, A. A. [Sloan-Kettering Inst., New York, N. Y.]: Studies on the metabolism of adenine. *Federation Proc.* 6: 517-522, Sept., 1947.—Dietary adenine, but not dietary guanine, is incorporated into the nucleic acids of the rat. Isotopic adenine containing N¹⁵ in each of the 1 and 3 nitrogens of the purine ring was fed to adult Sherman strain rats at levels of 200 mg. and 27 mg. per Kg. body weight per day for 3 days. Adenine, guanine and pyrimidines were isolated from the nucleic acids of the viscera; allantoin, urea, and ammonia, from the urine; and adenosinetriphosphate (ATP), from the leg and back muscles. The isotopic N of the ingested adenine was found in the adenine (13.7%) and guanine (8.2%) of the nucleic acids but not in the pyrimidine compounds: 27% was found in allantoin. Only a small amount of isotopic nitrogen was found in urea and ammonia. The incorporation of significant but small amounts of N¹⁵ in the ATP was found only at the higher dietary level of adenine. In similar experiments with N¹⁵ guanine a larger portion of the isotopic nitrogen was found in allantoin and, in confirmation of earlier work, no evidence of incorporation of dietary guanine into the tissue nucleic acids was obtained. Analysis of the location of the isotopic nitrogen in the guanine isolated from the nucleic acids when isotopic adenine was fed indicates that the adenine molecule is converted to guanine with the retention of the intact purine skeleton.—*C. Kensler, Ph.D.*

Greenberg, David M., & Schulman, Martin P. [Univ. Calif. M. Sch., Berkeley, Calif.]: Application of "metabolite antagonism" to cancer research. *Science* 106: 271-272, Sept. 19, 1947.

Greenstein, Jesse P. [Nat. Cancer Inst., Bethesda, Md.]: Enzymatic degradation of ribonucleic and deoxyribonucleic acids with an addendum on the effect of nucleates on the heat stability of proteins. *Federation Proc.* 6: 488-499, Sept., 1947.—A study has been made of the ability of fresh and dialyzed tissue extracts from the rat and mouse to deaminate and dephosphorylate several purines, nucleosides, nucleotides, and nucleic acids. Neither adenine nor cytosine is deaminated by any of the tissues studied. Only mouse kidney and liver are cap-

able of deaminating cytidine and cytidylic acid. All rat and mouse extracts readily deaminated adenylic acid, guanine, guanosine, and guanylic acid. Guanylic and uridylic acids are dephosphorylated to a greater extent than are adenylic and cytidylic acids. Dialyzed spleen extracts split off more dialyzable phosphorus from ribonucleic acid but no more ammonia than did fresh extracts. Dialyzed spleen extract split neither ammonia nor phosphorus from desoxyribonucleic acid. A wide variety of salts more than restore the ability of the dialyzed extracts to deaminate and dephosphorylate desoxyribonucleic acid; sodium fluoride and sodium bicarbonate in general inhibited activity in both fresh and dialyzed extracts. Certain salts also enhanced desoxyribonucleodepolymerase activity of dialyzed tissue extracts. Desoxyribonucleic acid, but not ribonucleic acid, has been found to prevent the heat coagulation of crystalline egg albumin at low salt concentrations.—*C. Kensler, Ph. D.*

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pyrimidine compounds are left as nucleotides. Phosphotungstic acid was used to separate uridine and uridylic acid quantitatively from cytidine and cytidylic acid. The pyrimidine nucleosides and nucleotides were assayed by measuring the growth (dry weight) of *Neurospora* mutant no. 1298 in a liquid basal medium. Adenine (or hypoxanthine) were assayed by the use of *N. mutant* no. 38,610. Guanine was determined colorimetrically by means of the phenol reagent.—*C. Kensler, Ph.D.*

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A wide range of spontaneous tumors exists. Lung tumors depend upon multiple genes with some evidence of linkage with known genes. Mammary tumors result from action of a "milk" influence, genes and hormones. Adrenal tumors may be produced and prevented by manipulation of sex hormones and diethylstilbestrol. Leukemia depends upon genes and some as yet unidentified maternal influence. Various non-

epithelial tumors have a complex genetic basis with no evidence of maternal influence. Various tumors show a relation to gene *d* for dilution, gene *A^y* for yellow coat color and to hybridization, being more numerous in cross-bred animals.—*Auth. Summ.*

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COMPLETE EXCISION OF PELVIC VISCERA FOR ADVANCED CARCINOMA

A One-Stage Abdominoperineal Operation with End Colostomy and Bilateral Ureteral Implantation into the Colon above the Colostomy.

ALEXANDER BRUNSCHWIG, M.D.

THE purpose of this report is to present an operation devised for the total excision of all pelvic viscera en masse for advanced carcinoma. This procedure represents the most radical surgical attack so far described for pelvic cancer and also would appear to be among the most radical of abdominal operations that have been carried out with some measure of consistency. The first operation was performed by the author on December 12, 1946, the second on December 26, 1946, the third on April 7, 1947. The experiences in these three instances afforded confidence to proceed with the operation in those patients with advanced cancer in the pelvis, who were suffering varying degrees of pain and other discomforts attributable to large masses of malignant tissue that had become infected, given rise to fistulas, and had previously received various forms of radiation therapy that had failed to control the growths. It is to be noted that no selection was exercised except, of course, that the disease be confined to the pelvis. The factors of age, nutritional status, physical constitution, and so on were not taken into account. It is also to be noted that not a single patient refused the operation even after detailed explanation of the extent of the procedure and emphasis on the permanent nature of the colostomy, that was also to be the site of urinary excretion.

OPERATION

The operation is as follows (Figs. 1 and 2):

Preoperative Preparation. Blood transfusions are given if necessary to bring the blood count and plasma proteins to within normal

levels. Vitamins C and K are administered. Castor oil is given in the evening on the third and second days and magnesium sulfate on the following morning. No cathartics are given within twenty-four hours before operation. Sulfasuxidine was administered for four or five days prior to operation; later 1 gm. a day of streptomycin by mouth was given for two days before operation instead of the sulfasuxidine. The day before operation, 8 gm. of sulfadiazine is given.

Anesthesia. Continuous spinal or intratracheal ether has been used.

At the beginning of the operation saline and then blood are administered intravenously.

Abdominal Phase.

1. The low midline incision extends a few centimeters above the umbilicus. The abdomen is palpated and inspected to confirm the absence of metastases.
2. The patient is placed in the Trendelenburg position and the bowels packed upward with laparotomy pads. The posterior parietal peritoneum over the bifurcation of the aorta is incised, these incisions being carried downward over the right external iliac artery. The right ovarian vessels and ligament are ligated and divided. The lymph nodes, and periauterial and perivenous tissue are dissected downward on the right side. The right hypogastric artery and vein near the bifurcation of the common iliac is isolated, ligated, and transected.
3. The mesosigmoid is divided over the left common iliac vessels and the sigmoid colon pushed upward. The left ovarian suspensory ligament and vessels are ligated and divided. The lymph nodes

From Memorial Hospital, New York, N. Y.
Received for publication, April 16, 1948.

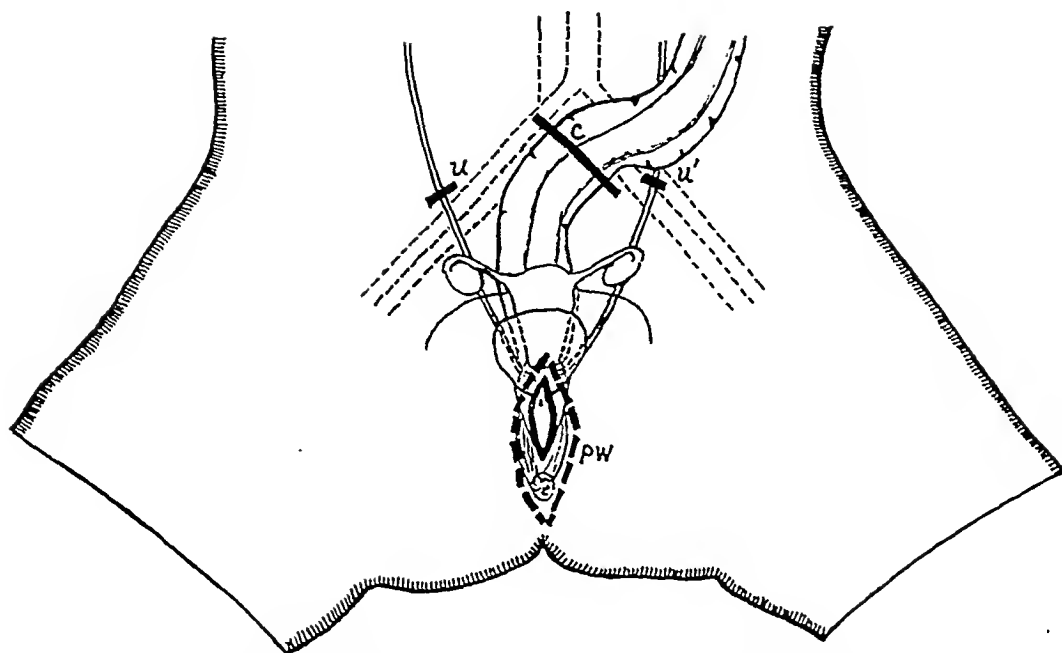


FIG. 1. Diagram showing levels of transection and incision in the performance of total resection of pelvic viscera. U, U', Levels of transection of right and left ureters respectively near the external iliac vessels. Sometimes the ureters are transected lower. C, Level of transection in region of upper pelvic colon. PW, Elliptical incision performed at second stage which encompasses the vulva and anus. In younger women the clitoris and labia minora are left in situ.

- and perivascular tissues of the left common iliac and external iliac vessels are dissected downward. The left hypogastric artery and vein near the bifurcation of the left common iliac vessel are isolated, ligated, and divided.
4. On the right side, the round ligament of the uterus is divided near the abdominal wall. The contents of the right obturator fossa and right side of the pelvis are so dissected as to mobilize these tissues en bloc mesially. The obturator vein is divided, but the obturator nerve is preserved and pushed laterally to lie freely near the right pelvic wall. The arteries and veins coursing from the right pelvic wall to the tissue that has been retracted mesially are ligated and divided.
5. The peritoneal reflection from the anterior abdominal wall onto the bladder is divided, and the latter separated from the symphysis pubis. The bladder is completely mobilized except for its attachments at the base.
6. The areolar tissues on the left side of the pelvis and in the left obturator fossa are completely dissected and mobilized mesially as described under "4" for the right side.
7. Both ureters are divided at a convenient level, well above any gross evidence of involvement by neoplasm. In mobilizing the ureters, care is exercised not to remove too much periureteral tissue. This tends to prevent necrosis of the ureters.
8. First one and then the other of the ureters is implanted into the sigmoid colon. The sites of implantation vary depending upon the redundancy of the sigmoid and the length of the ureters remaining. Needless to add, the implantations are made in such a manner as to avoid sharp angulations. In three instances in the series herein reported, the right ureter was implanted into the cecum. The ureteral implantations are carried out essentially according to the Coffey-I method.
9. The upper pelvic colon is transected and

- each cut end invaginated by a purse-string suture. The mesopelvic colon is divided with preservation of the blood supply to the sigmoid.
10. The pelvic colon is dissected away from the concavity of sacrum and mobilized completely down to the pelvic floor.
 11. At this stage, all the pelvic viscera are isolated and mobilized except for the attachments to the pelvic floor. The abdominal wound is closed, with the end of the sigmoid brought out through the midline incision. When the wound is closed the colostomy is opened. A hard-rubber tube drain extending into the pelvis is inserted in the lower angle of the wound.
- Perineal Phase.*
12. The patient is placed in the lithotomy position. The vaginal introitus is closed by continuous suture, and the anus, by a purse-string suture.
 13. Elliptical incisions are made to encompass introitus and anus and extend from the tip of the coccyx to below the clitoris which is preserved. The dissection is carried upward, and the levator ani muscles are divided.
 14. The pelvic contents, enmasse, are taken out of the pelvis from below (Fig. 3).
 15. The perineal wound is closed. The deeper soft tissues are approximated, and the skin is closed with interrupted chromic catgut sutures. Usually there is blood exuding from the large raw surfaces of the pelvic walls, so gauze packs are placed against the hollow of the sacrum. These are brought out through the posterior angle of the wound. A rubber tube drain is brought out through the anterior angle of the wound just below the clitoris.
- After Care.* Continuous gastric aspiration is carried out for seventy-two to ninety-six

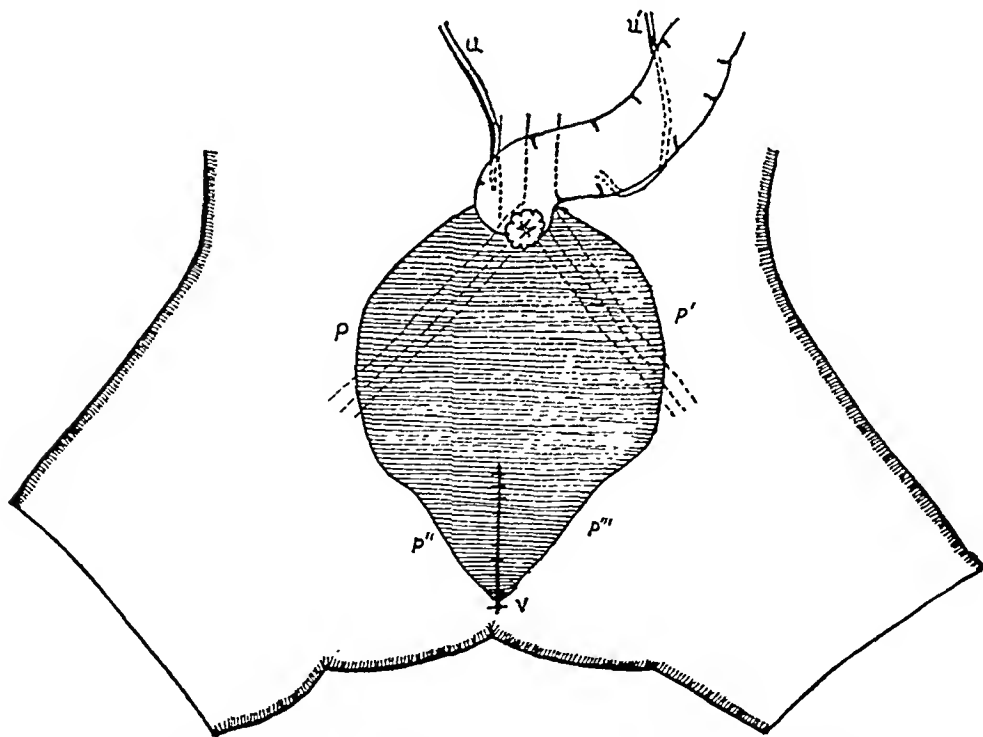


FIG. 2. Diagram showing conditions at end of operation for complete excision of pelvic viscera. The shaded area, P, P', P'', P''', indicates area of pelvis from which peritoneum has been stripped as well as pelvic viscera removed. The peritoneal stripping has extended above the level of the common and external iliac vessels. The midline colostomy is shown with U, U', both ureters implanted into the colon a short distance above colostomy.

hours, or longer, postoperatively and penicillin and streptomycin are administered for three to five days. Adequate fluid balance is maintained by venoclyses.

In two to four days, adequate quantities of urine are being discharged through the colostomy.

OPERATIVE MORTALITY

At this writing, twenty-two patients have been operated upon (Table 1). Five patients

are considered to represent the surgical mortality. This is, therefore, 23 per cent (Tables 2 and 3.) In view of the situations present in these unselected patients, the mortality in this original series is not considered excessive and would compare favorably with the mortalities attendant upon the initial attempts at gastrectomy for cancer, total pneumonectomy, pancreatoduodenectomy, combined abdominoperineal resection of the colon, and so on.



FIG. 3. Photograph of surgical specimen consisting of all pelvic viscera (Case 3) removed en masse for recurrent squamous-cell carcinoma of cervix, C, that has produced V, vesicovaginal fistula, and has invaded the wall of the pelvic colon with P, production of papillomatous growth into the lumen of the bowel. A, Anus; I, vaginal introitus; U, urethra; C, clitoris; B, urinary bladder; M, M', M'', entire anal, pelvic, and most of sigmoid colon.

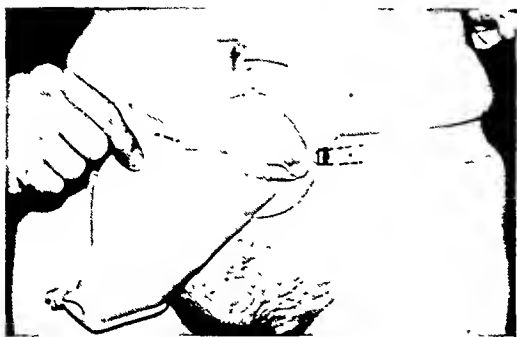


FIG. 4. Photograph of patient (Case 10) eighty-seven days after complete excision of pelvic viscera for advanced carcinoma of the cervix invading bladder and colon, showing the method of management of the "wet colostomy" by means of the Rutzen bag. Note the normal appearance of the skin. A rubber band secures the outlet of the bag and permits emptying of the latter as desired without breaking the hermetic seal to the abdominal wall. Patient remained in hospital seventeen days after operation; since discharge has resumed her usual household activities.

THE "WET COLOSTOMY"

At first the constant soiling from the colostomies was a formidable problem and at one moment threatened to discourage continued performance of the operation. The solution of this problem was possible by means of the Rutzen bag with its "cement" attachment to the skin, which keeps the skin in practically normal condition. The patients rapidly learn the management of the colostomy and this feature does not now present a serious problem (Fig. 4).

Shortly after operation, the discharges from the colostomy consist principally of urine; later, they are mostly liquid stool (due to admixture of urine and feces). At times clear urine is passed, resembling bladder urine voided normally.

IMMEDIATE RESULTS OF THE OPERATION

In view of the brief period since the procedure was initiated, no conclusions are yet warranted as to its status. As already stated, the operation was performed on patients with the most advanced stages of pelvic cancer—a procedure of desperation since all other at-

tempts to control the disease had failed. Because of the advanced stage of their disease, it is not to be anticipated that many, if any, of these patients will survive for very prolonged periods; metastases in the periaortic nodes, inguinal nodes, liver, lungs, bones, and elsewhere that were not appreciable at the time of operation, have probably occurred and will become manifest as time goes on. Two patients among those who have survived, did experience periods of relief and return to almost normal existence, but then developed metastases and have succumbed. On the other hand, of those surviving at this writing, not one has expressed the feeling that they would have preferred to have remained as they were and not to have had the operation. The latter statement, it is felt, expresses the present situation in regard to the palliative results of the procedure (Fig. 5).

SURGICAL PRINCIPLES DEMONSTRATED BY THE OPERATION

So far the experiences with the operation and several months' follow-up in some instances permit the following observations:

The extent to which modern pre- and post-operative supportive treatment permits extensive surgery is again demonstrated.

A colostomy with both ureters implanted into the colon above is a feasible procedure and affords a situation compatible with normal physical activity.

Complete deperitonization of the pelvis may be carried out and the small intestines permitted to descend into it without subsequent development of intestinal obstruction.

DISCUSSION

Although the procedure described here is a very radical one, the immediate mortality in an unselected series of patients, as previously indicated, was not inordinately high. It is to be recalled that for months to as long as a year prior to undergoing the operation all of these patients had been declared to be in the terminal stages of the disease, and that even for some time prior to this they presented all the usual criteria of "inoperability." Varying degrees of palliation have been at-

tained, for which reason the procedure is deemed justified, at least in the opinion of the author. With a measure of selection, the immediate surgical mortality should be reduced.

Another aspect also arises: it would appear that once carcinoma in the pelvis cannot be controlled by relative conservative measures, i.e., irradiation, with or without some standard type of operation, radical surgery may have something to offer and might well be

considered early in the stages of bladder and rectal invasion, rather than be postponed until the pelvic spread has become extensive.

SUMMARY

A surgical procedure is described for palliative excision of all pelvic viscera in patients presenting advanced pelvic cancer. Excretory functions of the urinary and alimentary tracts are possible by means of a colostomy with

TABLE 1.

SUMMARY OF PATIENTS WHO UNDERWENT TOTAL EXCISION OF PELVIC VISCERA (AS OF APRIL 10, 1948).

<i>Patient</i>	<i>Survived operation</i>	<i>Subsequent course</i>
1. N. C. (f.) 60 yrs. Ca. vagina	36 days	Died suddenly. Necropsy: cardiac (auricular) thrombosis; abdomen neg.
2. M. S. (f.) 46 yrs. Ca. cervix	5 days	Operative death; necropsy: peritonitis, pyelonephritis.
3. Grab. (f.) 45 yrs. Ca. cervix	8 months	Very good palliation. Returned to almost normal existence for 4 mos. Died of carcinomatosis.
4. Baret. (f.) 32 yrs. Ca. cervix	6 months	Living, well. Gained 30 lbs. Returned to full normal activities.
5. M. Sylv. (f.) 58 yrs. Recur. ca. corpus.	6 months	Living, well. Colostomy stenosed, but functioning well.
6. F. H. (f.) 47 yrs. Ca. cervix	7 months	Living, well. Returned to gainful occupation.
7. L. S. (f.) 38 yrs. Sarcoma uterus with retroperitoneal and omental metastases	4 months	Received palliation. Died of sarcomatosis. For brief period returned to work.
8. M. P. (m.) 46 yrs. Ca. sigmoid invading bladder	3 months	Palliation. Almost normal physical activity. Partial resumption of work.
9. M. L. (f.) 48 yrs. Ca. cervix	4 months	Living, no evidence recurrence. Gen'l physical condition not satisfactory because of inadequate nutrition received at home. No pain.
10. E. R. (f.) 40 yrs. Ca. cervix	4 months	Living, well; free from all pain. Normally active in household duties.
11. And. (f.) 52 yrs. Ca. cervix	5 days	Died suddenly; temp., pulse, resp., normal before death. Necropsy: entirely neg. except for old luetic aortitis.
12. T. M. (f.) 61 yrs. Extensive ca. vulva	42 days	Died after suddenly developing clinical signs of hemiplegia and coma. Complete necropsy neg. Perineal wound not yet completely healed but showed no evidence of having been cause of death.
13. Web. (f.) 35 yrs. Ca. cervix	2 months	Living, well. Free from pain. Almost normal physical activity.
14. Lamb. (f.) 55 yrs. Ca. cervix	9 days	Operative death. Necropsy revealed bilat. pneumonia. Patient required tracheotomy 4th day because of acute laryngeal edema.
15. C. W. (f.) 45 yrs.* Ca. cervix	1½ months	Living, well, receiving palliation. Gradually increasing physical activities.
16. Math. (f.) 44 yrs. Ca. cervix	16 days	Postoperative death, uremia. Necropsy not obtained.
17. Christ. (f.) 47 yrs. Ca. cervix	2 2/3 months	Living, well, receiving palliation but has metastases in left ileum.
18. Butt (f.) 59 yrs. Ca. cervix	1 month	Living, well. Since discharge from hospital is increasing physical activities.
19. Tirel. (f.) 58 yrs. Ext. ca. vulva	4 days	Operative death. Septicemia. Necropsy: Bilat. pyelonephritis.
20. Snit. (f.) 56 yrs.	2 weeks	Still in hospital. Satisfactory.
21. Bad. (f.) 48 yrs.†† Ca. cervix	4 months	Living, well. No complaints. Ambulatory.
22. Bruk (f.) 50 yrs.†† Ca. cervix	2 weeks	Still in hospital. Condition satisfactory.

* Patient operated upon by Dr. Thomas Walsh, Memorial Hospital.

† Patients operated upon by Dr. Michael Jordan, Memorial Hospital.

†† Excision of pelvic viscera accomplished in two stages one month apart.

bilateral ureteral implantation above the colostomy. This is not incompatible with normal physical activity.*



FIG. 5. Photograph of patient (Case 6), 47 years of age, taken February 2, 1948. On September 23, 1947, a complete excision of pelvic viscera was performed for uncontrolled carcinoma primary in cervix that had extended into bladder with vesicovaginal fistula and had infiltrated the wall of the pelvic colon. Previous treatment consisted of irradiation by means of roentgen-rays and intracervical application of radium. She has returned to her usual occupation in business and the only complaint (April, 1948) is a small persistent perineal fistula, biopsies of which on two occasions show no evidence of neoplasm. Colostomy function and care present no problems.

* *Acknowledgments.* The successful outcome in operations such as the described is dependent upon meticulous postoperative care. For this the writer desires to acknowledge the help of his several residents, Dr. Edward Camp (University of Chicago), Dr. Mason Morfit, Dr. Carlos Gutierrez,

TABLE 2.

SUMMARY OF OPERATIVE STATISTICS

Total number of patients operated upon	22
Postoperative deaths (Cases Nos. 2, 11, 14, 16, 19)	5
Per cent surgical mortality	23%
Deaths during operation	0
Average postoperative survival among those classified as surgical mortality	8 days

TABLE 3.

SUMMARY OF COMPLICATIONS IN FATAL CASES

Case No.	Complications
2.	Peritoncalization of pelvis was made. Ureteral catheters were inserted into each ureter at operation and brought out colostomy. Patient died of peritonitis; a loop of small bowel had herniated through an opening into reconstituted pelvic diaphragm. There was acute pyelonephritis.
11.	Patient's postoperative course was uneventful. After stating to her nurse that she felt quite well, on evening of the 5th day, she died suddenly. Complete necropsy failed to reveal the cause of death.
14.	On 4th day, developed acute laryngeal edema necessitating tracheostomy; following this, developed bilateral pneumonia. Succumbed on 9th day. Necropsy revealed the abdomen to be negative.
16.	Immediate postoperative recovery was satisfactory. Developed obstruction of colostomy, where the colon passed through abdominal wall. Intubation of the colostomy and finally incision of the fascia to permit wider opening was made. Following this urine was passed through sinus in pelvic wound and not through colostomy. Necropsy was not obtained but it was felt that repeated intubations of colostomy had caused detachment of implanted ureters. (These implantations were made just within the abdominal wall.)
19.	Had extensive resection of perineum for vulvar cancer invading rectum and base of bladder. The night of operation temperature was markedly elevated and remained high. Blood and spinal fluid cultures were positive for organism <i>Bacterium aerogenes</i> . At necropsy acute pyelonephritis was found.

Dr. Thomas Walsh, and Dr. Fernando Gentil, residents at Memorial Hospital, and the assistant residents on the service in Memorial Hospital at various times. The successful solution to the problems of colostomy management was due to the untiring efforts of Dr. Virginia K. Pierce, National Cancer Institute Trainee at Memorial Hospital.

PAPILLARY ADENOMAS OF THE LARGE INTESTINE

A Clinical and Morphological Study of Forty-eight Cases

DOUGLAS A. SUNDERLAND, M.D., and GEORGE E. BINKLEY, M.B. (TOR.)

AS their name implies, papillomas, or villous tumors, are composed chiefly of slender, finger-like projections or villi. They are derived from the mucous membrane of the large intestine to which they are attached by a broad base. They are comparatively rare. As described in the literature, their outstanding characteristics show them to be frequently of large size, and usually of solitary incidence; to have a tendency to broad, flat attachment to the bowel wall; and to occur almost exclusively in adults.

In 1899, Quénu and Landel published one of the first comprehensive studies of villous tumors together with four case reports. They called attention to the fact that the periphery is the most active site of growth and noted the difference in structure between the villous tumor and the adenoma. On the other hand, David,³ who presented eight cases of papillomas in 1925, emphasized the close relationship between papillomas and adenomas.

In two fairly recent studies,^{5, 12} of mucosal polyps of the colon and rectum, the papilloma has been considered not as a separate entity, but as an example of the growth variation to which all adenomas may be subject. Helwig, in his recent excellent study of 139 cases of single or multiple adenomas of the colon, found in 1460 consecutive autopsies, concluded that all adenomas have a basic resemblance and no practical significance can be attached to minor variations in structure and cells. Under minor variations of structure he included villosity of surface.

The potential capacity of villous papillomas (as a group) to undergo carcinomatous change has always been in doubt. Although all authors have viewed the tumors with suspicion, only a small number of the

cases studied have revealed foci of carcinoma in the resected specimens. Thus David,⁴ reported that he found invasive carcinoma in two of twenty-seven cases of papilloma; that cancer did not arise in any case subjected to repeated fulguration; and that no cancer occurred after removal of the tumor.

Because of our repeated observation of certain peculiarities of incidence, growth, and clinical course of this type of adenomatous polyp, we have been prompted to survey the present and past cases occurring on the Colon and Rectum Service at Memorial Hospital. Since previous studies have been based on purely morphological findings, we hoped that a correlation of the clinical characteristics and course with the gross and microscopic morphology would enable us to determine the actual carcinomatous potentiality of this tumor and whether or not there is practical justification for viewing it as a clinical entity.

MATERIAL AND METHODS

The material was selected from a total of 3356 tumors of the large intestine that were treated on the Colon and Rectum Service of Memorial Hospital during the twenty-one-year period from July 1, 1926 to July 1, 1946. Only those polyps that were of villous structure and of predominantly benign morphology, as determined by microscopic examination, were selected for study. No polyp whose surface was only coarsely lobular was included, regardless of its size. Several tumors that appeared in the gross to have a papillary surface were excluded when microscopic study showed only arborescent lobulation without projecting surface villi.

Care was also taken to rule out tumors that could be considered carcinoma either on clinical or microscopic grounds when first seen: (1) that, on examination after initial removal, showed gross or microscopic replace-

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Received for publication, February 13, 1948.

ment of the polyp by invasive carcinoma; (2) that showed diffuse carcinomatous epithelial change, without invasion, and so could be regarded as low-grade, noninfiltrating papillary carcinoma. Included, however, were those in which only microscopic foci of cytological (in situ) carcinoma were found in an otherwise structurally benign polyp.

In all, forty-eight tumors were found to fulfill these criteria and these form the basis of this report.

For microscopic comparison, nine adenocarcinomas arising in papillary adenomas were studied in detail. These were not merely carcinomas with a grossly papillary surface but carcinomas in which substantial portions of benign polyp with a microscopically demonstrable villous surface persisted. In addition, numerous cases of single and multiple adenomas and several of familial polyposis were reviewed.

Although most of the material was obtained prior to the beginning of the study, all removed portions of each tumor were available for detailed analysis because of the existing policy of cautery-snare removal (rather than fulguration) and of the standard laboratory technique of description and section taking. Multiple microscopic sections had been made, care being taken that these were perpendicular to the surface, so that the base could be adequately studied (in one of the more recent cases as many as thirty-seven blocks were taken from a single specimen). All surgically resected tumors, as well as all lymph nodes that could be found by careful search, were carefully dissected and multiple sections made through the tumor and bowel wall. In all, including biopsy specimens, more than 400 sections of papillomas were examined in detail microscopically.

After the forty-eight cases had been selected, all sections of these were reviewed microscopically, without any knowledge of the clinical course. The following features were determined systematically in each section and tabulated:

1. Nature of attachment of the polyp to the bowel wall—presence or absence of inflammatory infiltration of stalk, with types of cell appearing.

2. Villi—contour; presence or absence of capillary engorgement, hemorrhage, edema, cell infiltration, tumor invasion; character of epithelium, presence and degree of variation—papillary tufting, secondary gland formation, stratification, and amount of mucus secretion.

3. Glands—degree of enlargement and distortion; amount of mucus secretion; presence or absence of mucous cysts; character of epithelium with presence and degree of variation, as above.

4. General cellular structure of epithelium—presence and number of mitoses; nuclear and cellular apolarity; nuclear size, shape, and staining characteristics; presence or absence of enlarged nucleoli; size and shape of cells with staining characteristics of cytoplasm.

A parallel study was made of the nine cases of carcinoma occurring in papillary adenomas, and the results of the two series were compared. After the microscopic study was completed, a chronological comparison was made between these findings, the clinical characteristics of each papillary adenoma, and the clinical course of each patient.

CRITERIA OF CARCINOMATOUS CHANGE

Microscopically, the criterion of cancerous transformation was loss of nuclear polarity accompanied by variation in nuclear size, shape, chromatin arrangement, and content. With one or two exceptions this nuclear apolarity was associated with apolarity of the cells as a group, but the reverse—cell apolarity without nuclear apolarity—was never found. Invasion of the stalk of the polyp was, of course, accepted as irrefutable evidence of carcinoma. However, unless the muscularis mucosae be penetrated, it is almost impossible to demonstrate stalk invasion with certainty. Likewise, true stratification is very difficult to differentiate from artifact unless the cells have lost their polarity.

Increase in the intensity of the nuclear staining reaction and a tendency of the cytoplasm to basophilia, regarded by Schiller as one of the criteria of malignant change, are not adequate evidence. These undoubtedly denote change in the character of cell growth,



FIG. 1. *Normal rectal mucosa. The cells of the surface epithelium are longer and narrower than those lining the glands. The nuclei are somewhat elongated and tend to occupy the central portion of the cells rather than the base. There is a definite junction between the surface and the gland orifice.*

but their presence or absence is too dependent on variations in staining technique to make them of value. If they be evoked as criteria, very few mucosal polyps would escape the diagnosis of carcinoma.

Enlargement of the nucleoli frequently accompanied the other nuclear changes. When present such nucleoli were regarded as corroborative evidence, but, since they are not easily found in many fully developed rectal carcinomas, their absence was not considered significant when the other characteristics were present.

STRUCTURE AND GROWTH

From observations made in the course of this microscopic study, it became evident that there is a fundamental structural difference between papillomas and adenomas. Before considering these observations in detail, however, it may be well to call attention to the normal structure of the epithelium of the mucosa of the large intestine.

This can be divided into two portions: surface epithelium and underlying mucus-secreting glands. Both portions are of similar embryological origin—although there is some difference of opinion about the development of the glands—whether they are formed as downgrowths of the surface epithelium or by fusion of the tips of villi which were originally present and subsequently disappeared. In well-preserved specimens of the adult colon and rectum, differences in appearance can generally be noted between the cells of the covering surface epithelium and the cells lining the lumina of the underlying glands (Fig. 1). The latter are almost entirely mucus-secreting goblet cells with a nucleus situated in the base of the cell. The surface cell has a striated, cuticular border and tends to be narrower and more elongated. The nucleus often shows a slight lateral compression and is more often situated in the central portion than in the base of the cell. Occasionally, ad-

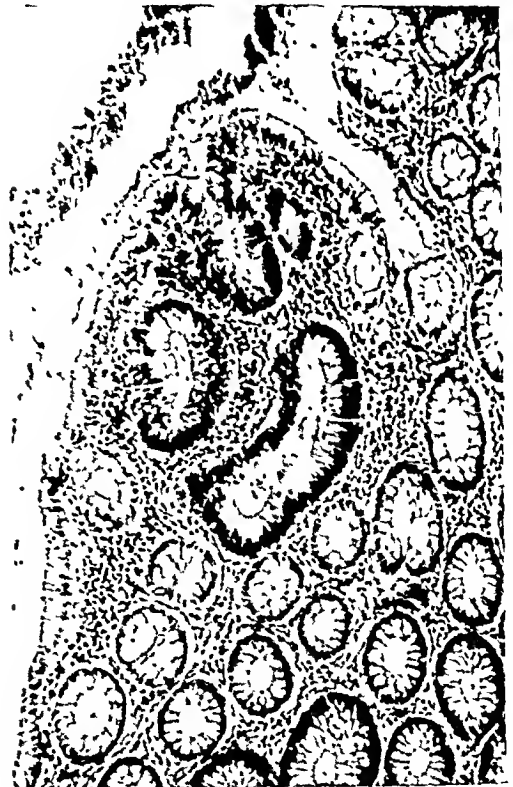


FIG. 2. *Early adenoma, from a case of familial polyposis. The site of origin in the peripheral portion of glands is well demonstrated. The covering epithelium appears normal over the surface of the adenoma.*

jacent cells will have the nuclei in different positions—some in the base and some in the central portion—giving the false impression of stratification. There is generally less mucus secretion in the surface cells than in those forming glands, and a definite junction between the surface and the glandular orifice can be identified. Occasionally, however, this junction is rather difficult to identify when the cells of the surface epithelium secrete an excessive amount of mucus.

Microscopic study of areas of mucosal hyperplasia of large and small adenomas, and of the adenomas of familial polyposis, gives the impression that these generally originate in the epithelium lining the gland lumen, either close to the surface or in the mid-portion (Fig. 2) and only seldom in the deepest portion. Elongation and lateral compression of the epithelial cells with a variable degree of increased intensity in the staining reaction comprise the initial changes. The gland as a whole becomes enlarged and distorted. Mucus secretion may be increased, decreased, or remain unchanged. Adjacent glands are involved progressively. The superficial portion of each gland is affected first, often making a sharp line between the normal and neoplastic epithelium in the same gland. At the lateral border of the adenoma there is a sharp transition between the involved glands and those of the adjacent normal mucosa (Fig. 3).

In small adenomas the covering epithelium shows little change from normal. Apparently it does not participate in the active glandular proliferative process, but merely forms a containing membrane for the underlying, expanding tumor. The covering epithelium of the adjacent normal mucosa is continued over the surface of the adenoma, and when not completely eroded can be easily identified as a normal-appearing structure in contrast to the distorted proliferating glands beneath (Figs. 4 and 5).

In larger adenomas the glands appear to be increased in both size and number and may assume bizarre, convoluted, branching patterns owing to the rapid reproduction of the lining cells. Although the epithelial covering in some places shows active growth that

results in villous processes, this is exceptional, and in most surface areas the junction of the gland orifice with the normal-appearing covering epithelium can be easily identified.

In the papillomas studied in this series, the picture is different. Here the epithelial covering layer shows the greatest departure from normal. The tumor is composed of villous processes, covered by epithelium that shows definite similarity to the covering epithelium of the normal mucosa. This epithelium is continuous with that of the glands beneath and there is no sharp junction between the surface epithelium and that of the deep glands lying on the muscularis mucosae. In general, the epithelial cells of the villi evidence less mucus-secreting activity than do those of the glands, but this is not a constant finding any more than it is in the surface epithelium of the normal mucosa. The cells tend to be more elongated, the nuclei more compressed. As in the covering epithelium of the normal bowel, the nuclei are situated in both the base and the center of the cell and



FIG. 3. Adenoma—showing junction with normal mucosa, in the lower part of picture. There is an abrupt change in the appearance of the glands, with enlargement, distortion, elongation of cells, and intensified staining reaction.

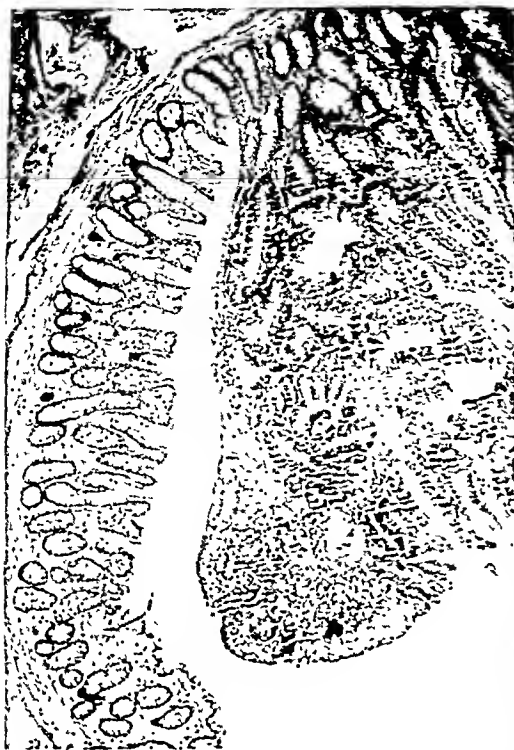


FIG. 4. Adenoma—junction of polyp with normal mucosa of stalk. Marked distortion of glands, with abrupt line of demarcation.



FIG. 5. Same as Fig. 4. Higher magnification showing normal-appearing surface epithelium continued over polyp, in sharp contrast to the distorted underlying glands.

often give the false impression of stratification.

It is in the lateral portion of the tumor, at the point of junction with normal mucosa, that the most striking structural difference between papillomas and adenomas is seen. In papillomas, it is the surface epithelium, not the glandular portion, of the mucosa that seems to be affected first. At the lateral border of the tumor, the initial change is a sharp difference in the appearance of the surface cells (Fig. 6). This change in morphology, analogous to the change in the glandular epithelium seen in adenomas, consists of increased staining intensity, elongation, and compression. The affected epithelium is thrown up into small papillae that project into the lumen of the bowel. Beneath this changed surface the glands at first appear normal (Figs. 7 and 8). As the central portion of the tumor is approached, a progressive downward involvement of the glands occurs, with evidence of disproportionately rapid growth of the surface epithelium that is thrown up into longer projections (Fig.

9). In most cases this continues until the entire thickness of the mucosa is involved. In

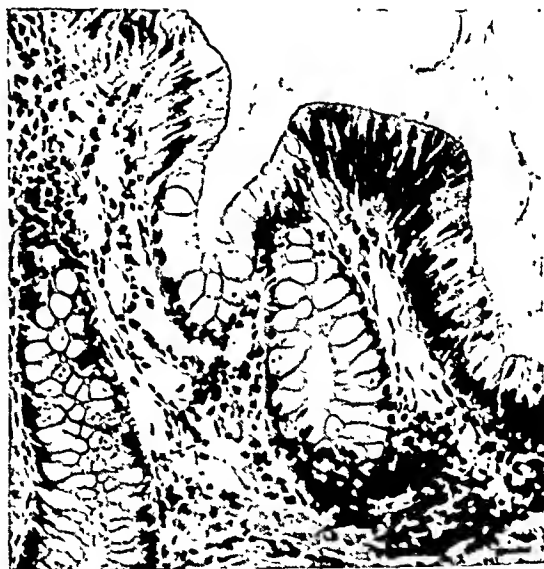


FIG. 6. Papillary adenoma. Junction of lateral margin of tumor with normal mucosa on left. Abrupt change in appearance of surface epithelium—elongation and compression of cells and intensified staining reaction.



FIG. 7. Same as Fig. 6. Lower magnification showing projection of surface papillae composed of changed surface epithelium. Underlying glands are not involved.



FIG. 8. Another papillary adenoma showing the same marginal characteristics as Fig. 7.

smaller tumors, however, it is not uncommon to find the deepest portion of the glands appearing normal throughout the base.

These observations introduce the concept that the difference between papillomas and adenomas is not merely one of superficial surface configuration, but the more fundamental one of difference in method of growth. Whereas the adenoma is a tumor of mucosal glands, with little if any involvement of the surface epithelium, the papilloma is the reverse—a tumor primarily of the mucosal surface epithelium with resultant secondary glandular changes.*

This concept is strengthened by consideration of the nature of the bowel-wall attachment of each type of tumor. Minute adenomas project only slightly above the surface of the surrounding mucosa. As they grow larger, they develop a pedicle comprised of dragged out muscularis mucosae and submucosal tissue carrying the blood supply of the tumor. This pedicle is considerably smaller in diameter than the tumor it supports and is covered by normal mucosa. In

still larger adenomas the glands arborize from a central stalk and form multilobular masses. The largest of these adenomas may have the configuration of large, thick-stemmed mushrooms. Even in these, however, the entire tumor projects from a central pedicle.

Papillomas, on the other hand, have a broad base and primarily flat attachment. In many portions of the tumor the individual villi and underlying glands arise and project directly from the muscularis mucosae, which is in the normal position parallel to the plane of the musculature of the wall. In other portions, groups of villi are elevated above the surrounding surface and spread out, fanlike, each group supported by a short pedicle composed of dragged out muscularis mucosae and submucosal tissue. Several such pedicles, either singly or grouped in close proximity, occur in the large tumors; but the pedicles are always covered by adjacent areas of tumor, in contrast to those of adenomas. A true pedicle, covered by normal mucosa and supporting the entire tumor, was noted in only two of the papillomas, the smallest in the series; and in each of these, the diameter of the pedicle was only slightly smaller than that of the tumor it supported.

It is generally accepted that a tumor of

* Since completion of this study, the same observation has been made by Cuthbert E. Dukes: An explanation of the difference between a papilloma and an adenoma of the rectum. *Proc. Roy. Soc. Med.* 40: 829-830, Nov., 1947.

the large intestine develops a pedicle because of the peristaltic squeezing action and the propulsive dragging effect of the passage of fecal material through the lumen. Hence, if it is not fixed to the muscular wall, any tumor of the mucosa or submucosa that projects into the lumen and grows to an appreciable size, will eventually become pedunculated. This is often the case with hypertrophied mucosal lymph follicles and submucosal lipomas and myomas. The mere pro-

jection of any rounded mass from the wall seems to act as a foreign body and the activity which it elicits is often forceful. Not uncommonly, as reported in the literature and observed by us, peristaltic action will be so violent as to avulse a polyp from its pedicle and expel it from the rectum with the feces.

Presumably, papillomas are subjected to the same peristaltic action as adenomas and, if the method of growth were the same, it would be expected that they would be



FIG. 9. Same tumor as Figs. 6 and 7. Shows progressive increase in length of villous projections as central portion of tumor is approached. Note the relatively normal appearance of the glands at the base, even toward central portion of the tumor.

dragged out on a pedicle in a similar manner—because the clinical course of the present series gives adequate evidence that they are generally present for a long period of time.

This difference in the attachment of papillomas and adenomas can be explained only by the difference in method of growth. In the papillomas the rapidly proliferating surface epithelium between the gland orifices is dragged out by peristaltic action to form multiple papillary projections. These become attenuated to form villi, with cores of mucosal connective tissue carrying the blood supply. The adenomas, however, being compact masses of enlarged glands enclosed by a limiting membrane of normal covering epithelium, are dragged out in toto, so that progressive lengthening of the pedicle causes progressive constriction of the base.

It might be argued that the absence of pedunculation can be explained by the fact that, since papillomas generally occur in the rectum, which is a more fixed structure than the colon, they are less subjected to violent peristaltic action. In controversion, adenomas with long pedicles actually do occur in the rectum as well as in the colon.

Further evidence for primary surface, rather than glandular, growth is the tendency of papillomas to progressive lateral spread. As noted by others and us, multiple recurrence is a typical feature—not always in the exact site of the lesion that was previously removed but in contiguous portions of the mucosa. In some instances the area of recurrence is so extensive that it seems as if there might be a regional sensitization to surface new growth. Whether this lateral surface spread is accomplished by a change in already existing cells or by the actual replacement of normal cells by neoplastic ones cannot be determined.

While the characteristic surface growth and spread clearly differentiates papillomas from adenomas, there is evidence that they are of common origin, and that the difference in type of growth is a secondary developmental phenomenon rather than a difference in the actual site of origin. In the first place, although minute adenomas are not uncommon, we have not observed a minute papilloma and do not know of any that have been reported elsewhere. Secondly, although the surface proliferation predominates, there



FIG. 10. *In situ* carcinoma in a papillary adenoma. This demonstrates an abrupt line of demarcation between malignant and benign areas. In the central portion both types of structure can be seen within a single gland. FIG. 11. Minute area of carcinomatous change in a papillary adenoma. This was the only focus found in this block, and is not sharply delineated from the surrounding areas. FIG. 12. *In situ* carcinoma in a papillary adenoma. The area of malignant transformation merges gradually with the adjacent benign areas.



FIG. 13. *Carcinomatous change occurring in the surface epithelium of a villus in a papillary adenoma. Note sharp contrast with adjacent villi of benign structure.*

is always some degree of underlying glandular involvement. Thirdly, in this series the papillomas were found in an older age group than were the adenomas and were all of large size, suggesting that papillomas may develop from adenomas. Fourthly, papillomas are occasionally associated with mucosal adenomas; they may or may not originate coincidentally. Finally, when carcinoma arises in a papilloma, it is generally the glandular portion of the tumor that is first involved and not the surface epithelium of the villi.

For these reasons, we believe that the more exact name for these villous tumors is papillary adenoma rather than papilloma, and this term will be used hereinafter.

No indications of etiology were obtained from this microscopic study.

CARCINOMATOUS CHANGE IN PAPILLARY ADENOMAS

In twenty-six of the papillary adenomas in this series, microscopic examination revealed areas of in situ carcinoma in the original tumor. The location of these areas with-

in the papillary adenoma varied considerably. In ten tumors in situ carcinoma was found in the superficial portion; in five, at the base; in eight cases it occurred in both the superficial and deeper portions; in two, there were minute foci scattered diffusely throughout the papillary adenoma; and finally, in one, the carcinoma arose in an isolated segment of the papillary adenoma, separated from the rest of the tumor by a strip of normal mucosa. There was also considerable variation in the sharpness of delineation of the area showing carcinomatous change and the adjacent areas having benign structure. This is well shown in Figs. 10, 11, and 12.

In most instances the areas of carcinomatous change were confined to a single localized portion of the polyp. With two exceptions this change was in the glandular portion of the tumor, rather than in the surface epithelium of the villi. In one of the two exceptions a single villus was involved (Fig. 13). In the other, several adjacent villi were affected. In this case the carcinomatous transformation consisted of nuclear change only (Figs. 14 and 15).

The statement has frequently been made in the literature that a negative biopsy made from the peripheral portions of a polyp is no guarantee of the benignity of its entire structure. This observation is reiterated here. In only seven cases of this group did the initial biopsy reveal the carcinoma. In ten, it showed benign structure; in one, atypical epithelial changes only. Eight tumors were not subjected to biopsy prior to their removal.

In addition to these twenty-six cases which showed areas of carcinoma in the original specimen, there were seven others in which carcinoma appeared later, in a recurrence at the site of the original tumor. In these cases it was generally impossible to determine the exact point of carcinomatous change within the papilloma.

Of these thirty-three cases (68.7 per cent of the total) which, early or late, showed in situ carcinoma, nineteen (39.5 per cent of the total) developed invasive carcinoma—infiltrating the muscular wall of the bowel, with or without metastases. Eleven were ade-



FIG. 14. *Carcinomatous change occurring in the surface epithelium of a villus. Here the change consists of nuclear variation only. The cells still maintain their polarity and all rest upon the basement membrane. Note the marked difference in the orderly appearance of the epithelium of the adjacent villus.*

FIG. 15. *Villi adjacent to those shown in Fig. 14. Under higher power the nuclear abnormality is more clearly shown.*

nocarcinomas, grade II or III in histological malignancy, and had no features to differentiate them from any other adenocarcinoma of the large bowel mucosa. Eight (42.1 per cent of the invasive carcinomas) were colloid carcinomas. This is a much higher proportion than is found in carcinoma of the rectum as a whole: Thus, only twenty-nine colloid carcinomas (7.7 per cent) were found in 374 consecutive cases of rectal and sigmoidal carcinoma seen by the Colon and Rectum Service of Memorial Hospital from 1931 to 1935 inclusive; and only twenty-three, or 9.6 per cent, in 239 specimens from consecutive single-stage abdominoperineal resections.

This interesting observation made us speculate whether the increased incidence of the colloid type of carcinoma was due to excessive mucus production by the polyp, but microscopie corroboration could not be found. The degree of mucus secretion varied

markedly in different portions of the individual tumors, and gradations from little or none to excessive amounts were seen just as frequently in those tumors that remained benign and those that developed ordinary adenocarcinoma, as in those that developed colloid carcinoma. The same was true for cystic dilatation of mucus-filled glands so frequently seen in adenomas.

The evolution of carcinoma in each of these tumors will be detailed further in the section devoted to Clinical Course.

INCIDENCE

The comparative rarity of papillary adenomas, repeatedly pointed out in the literature, is substantiated by the present study. Thus, 346 cases of single and multiple adenomatous polyps were encountered among 3356 benign and malignant tumors of the large intestine treated on the Colon and Rectum Service from July, 1926 to July,

1946. The forty-eight papillary adenomas comprise only 1.4 per cent of the total group and 13.9 per cent of the polyps.

Table 1 gives the age and sex incidence. There was almost equal distribution between the sexes—twenty-five males and twenty-three

the rectum and sigmoid on the Colon and Rectum Service at Memorial Hospital, the average age was 55.1 years. This is about the average age reported elsewhere.

Thus it is evident that papillary adenomas occur not only in an older age group than do adenomatous polyps in general, but also in an older age group than does carcinoma.

All the patients were of the white race: twenty-six were American-born, four Russian, three each German and Swedish, two each Italian, Canadian, Austrian, and Hungarian, and one each Roumanian, Jugoslavian, Polish, and English.

No definite hereditary factor was demonstrable. Four parents had died of cancer, one each of the rectum, of the stomach, of the throat, and of adamantinoma. (Incidentally, the patient whose parent had cancer of the rectum was among the youngest in the group—41 years old.) One aunt had had cancer of the breast, as had two siblings of each of two patients. In the remainder there was no family history of cancer.

TABLE 1

INCIDENCE OF PAPILLARY ADENOMAS BY AGE AND SEX

Age	Male	Female	Total
30-39	1	1	2
40-49	2	3	5
50-59	8	2	10
60-69	4	12	16
70-79	9	4	13
80-89	1	1	2
TOTAL	25	23	48

Sex	Average Age	Oldest	Youngest
Male	63.61	81	37
Female	61.71	81	35
Entire group	62.91	81	35

females, approximately the same incidence as for other mucosal tumors of the large intestine. The average age was 62.9 years, the youngest, 35 and the oldest, 81. The largest single group, chronologically arranged, occurred between the ages of 60 and 69 years.

This age incidence is at variance with that for the other mucosal adenomas observed by us and with that reported elsewhere for polyps. The average age of our 297 patients with adenomas was 54.5 years—more than eight years younger than those with papillary adenomas. Martin reported the average age incidence of polyps to be 45.3 years; Struthers, 46. The polyps considered benign by Swinton and Warren occurred in patients averaging 53 years; those considered malignant, 57.7. In Helwig's series, the largest single group occurred between the ages of 61 to 70 years. However, this series was composed of cases obtained at autopsy and does not necessarily reflect the age of clinical incidence of the adenomas—merely the age of incidence of the disease that caused the demise.

In 374 consecutive cases of carcinoma of

GROSS MORPHOLOGICAL CHARACTERISTICS

All the tumors had a papillary or combined papillary and finely lobular surface, varying in color from pinkish-gray to dark hemorrhagic red. One showed a small area of superficial ulceration and contained a focus of in situ carcinoma. All except two were attached to the bowel wall by a broad base. Both of these exceptions were 4 cm. in diameter and grew from short, thick pedicles and both showed microscopic foci of in situ carcinoma in the base; but neither recurred after removal.

With the exception of the three that were beyond reach of the examining finger, all but eight were so homogeneously soft to palpation that it was extremely difficult to determine their extent by this means alone. These eight tumors had small areas of induration; on removal, six showed areas of in situ carcinoma; one showed a small focus of in situ carcinoma in the biopsy but none in the specimen resected later; the other showed no carcinoma during the first year following removal—then was lost to follow-up.

Forty-one with solitary lesions have de-

veloped no other known rectal or colonic tumors to date. Two had a co-existent carcinoma situated above the papilloma; in one, the cancer was in the sigmoid; in the other, the descending colon. Two cases had several adenomas in the adjacent bowel when first seen. Three others subsequently developed minute adenomas: two, single; the third, multiple.

LOCATION AND SIZE

As a means of definite location, the rectum was arbitrarily divided into four portions: lower, mid-, upper, and rectosigmoid. The lower rectum was designated as that portion 0 to 4 cm. above the mucocutaneous junction of the anus; mid-rectum, 4 to 8 cm.; upper rectum, 8 to 12 cm.; and the rectosigmoid, the region of the peritoneal reflection, 12 to 15 cm.

All except one of the papillary adenomas occurred in the rectum: lower, fourteen; mid-, twenty-two; upper, nine, and rectosigmoid, two. In the remaining case the lesion was situated in the lower portion of the sigmoid colon 18 cm. above the anus. The site of origin of these papillary adenomas is in marked contrast to the location of the adenomas of Helwig's series, for these were more common in the sigmoid colon than in the rectum.

The right, left, anterior, and posterior walls were about equally affected. There was no constant relationship between the tumor site and the location of the valves of Houston. There was no correlation between the location of the tumor and subsequent carcinomatous change.

The papillary adenomas varied in size from 3 to 12 cm. in transverse diameter, the majority measuring between 4 and 6 cm. Twelve involved more than half the circumference of the bowel wall, and three of these were annular. The average duration of symptoms in these twelve cases was 36.4 months compared to 28.5 months for the entire group; seven had had symptoms for two or more years. This would indicate that the large size of these tumors is due primarily to the duration rather than to the rapidity of growth. Areas of carcinoma were subse-

quently found in nine, or 75 per cent, of these large tumors—a slightly higher incidence than that for the total group.

SYMPTOMS

As shown in Table 2, bleeding was the most common symptom. Next in frequency were diarrhea and excretion of mucus. Characteristically, the diarrhea was most severe in the morning. Owing to the large surface area of these tumors, a large amount of mucus may be secreted by them. Presumably, this accumulates in the rectum during the sleeping hours, and causes urgency when the patient awakens.

Protrusion of the mass through the anus occurred in nine of the fourteen patients whose lesions were situated in the lower rectum, but this was the initial symptom in only one case. There was no correlation between weight loss and the subsequent development of carcinoma but both the patients who complained of anal pain later developed infiltrating cancers. The papillary adenoma was discovered on routine rectal examination in the two patients who had no symptoms.

The duration of symptoms varied from a few weeks to ten years (Table 2). Although the average duration was 28.5 months, the largest single group of patients had symptoms for six to eleven months.

Before their admission to Memorial Hospital, nine patients had had fulgurations, cautery-snare removals, or surgical excisions elsewhere. In all instances the procedure was followed by early recurrence. In five instances the removals were multiple; in one, there had been seven removals in the course of eight years. Five of these nine patients later developed cancer.

TREATMENT

The treatment of papillary adenomas has been discussed in another article² and will be only briefly summarized here. When possible, the smaller, low-lying lesions were excised surgically with suture ligation of the base. The larger ones and those situated higher in the rectum were removed by the cautery snare, in single or multiple stages, depending upon the extent of mucosa involved. In most

TABLE 2
SYMPTOMS

<i>Incidence</i>	<i>Initial</i>	<i>Total</i>	<i>Duration</i>	
Bleeding	22	30	No symptoms	2
Diarrhea	9	20	Less than 6 mos.	4
Mucus excretion	13	17	6 mos.—11 mos.	13
Protrusion of tumor	1	9	12 mos.—17 mos.	4
Constipation	1	9	18 mos.—23 mos.	3
Weight loss	0	4	2-3 yrs.	7
Tenesmus	0	3	3-4 yrs.	3
Anal pain	0	2	4-5 yrs.	3
Anal irritation	0	2	5-6 yrs.	3
Increased flatus	0	2	6-7 yrs.	1
Soft stools	0	1	7-8 yrs.	1
No symptoms	2	2	8-9 yrs.	2
	—		9-10 yrs.	1
	48		10 yrs.	1
				—
				48

instances this procedure was supplemented by irradiation. Radical resection of the rectum was performed in those cases showing carcinomatous change when the patient's general condition was considered to be good enough to withstand the procedure. It must be remembered that some were treated many years ago, before the modern improvements in surgical technique, pre- and postoperative care, and use of plasma, sulfonamides, and other antibiotics, hence, the operability rate was not so high as at the present time. Those with carcinomatous change that were not treated by resection were irradiated.

Recently, proctosigmoidectomy, of the type described by Bacon, has been performed in two cases discussed in detail later. Both were performed less than six months ago and as yet the operation cannot be evaluated. This limited surgical procedure has been employed because no node invasion has been found in any specimen studied unless there was also penetration of the muscular wall of the bowel.

CLINICAL COURSE

Two outstanding features are evident in the clinical course of the patients with papillary adenomas: the extreme unpredictability of the clinical course, and the propensity of the tumor to repeated local recurrence. Because of this unpredictability, generalization

is impossible; each case must be considered briefly. To render this presentation more facile, the cases have been subdivided into four groups:

Group 1. Twenty-six cases in which the original tumor showed areas of in situ carcinoma.

Group 2. Seven cases in which carcinoma developed at the site of the original tumor, after this had been removed.

Group 3. Ten cases that have developed no carcinoma to date.

Group 4. Five miscellaneous cases.

Group 1. Eight patients of this group were treated surgically. In two, the tumor was removed from below by local excision and suture ligation of the base; one was pedunculated. Both these patients have remained free of recurrence to date, four and one-half and sixteen years respectively.

Two patients were subjected to single-stage abdominoperineal resection. The first of these had had an initial partial cautery-snare removal; the specimen showed small, superficial foci of carcinoma. The resection was performed sixteen months later; study of the specimen showed the papillary adenoma to be benign throughout, and sharply delimited at its base by muscularis mucosae (Fig. 16). The patient has remained free of tumor to date—more than two years after operation.

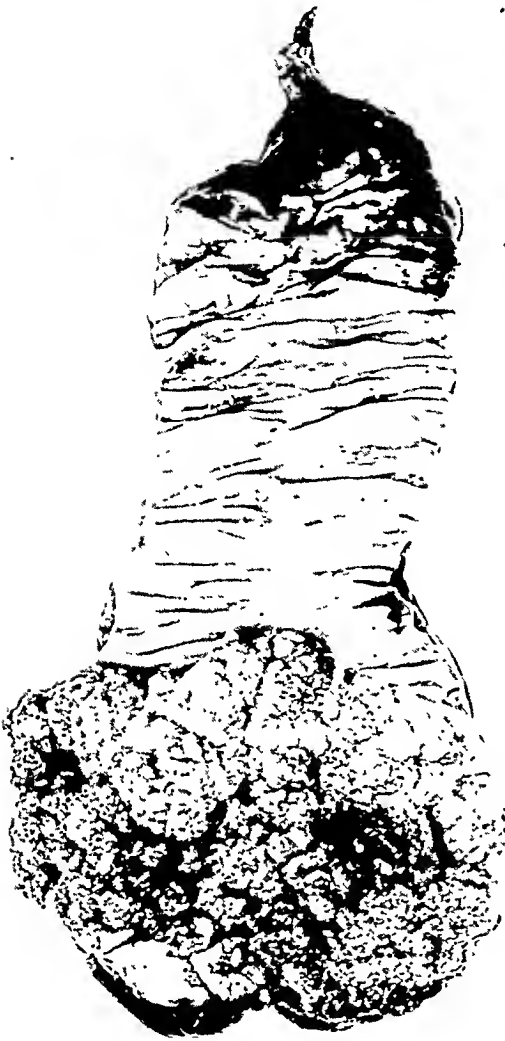


FIG. 16. *Papillary adenoma. Gross surgical specimen. The tumor measures 10 cm. in diameter and is of benign structure throughout.*

The other case was treated here first by roentgen rays plus cautery-snare removal followed by radium-applicator therapy. Again the area of carcinoma was superficial. Several months later there was a recurrence that, on biopsy, was found to be an infiltrating adenocarcinoma; resection was performed (eight months after he first came to Memorial Hospital). The rectal wall in the surgical specimen was invaded by carcinoma. At one point there was lymphatic invasion in the perirectal fat but no lymph-node involvement was demonstrable. Inguinal lymph-node metasta-

ses appeared fourteen months postoperatively and were proved by aspiration biopsy. The patient died of terminal uremia, thirty-four months after operation.

Two patients had perineal resection after preliminary loop colostomy. Previously one had had three excisions elsewhere with recurrence each time. An initial partial cautery-snare removal showed a superficial area of carcinoma. The two-stage surgical procedure followed immediately. The resected specimen showed atypical changes but no carcinoma. The patient remained free of recurrence until death from pneumonia five years later. Examination of the other patient's tumor after initial cautery-snare removal showed multiple minute foci of carcinoma in both the periphery and base. During the ensuing three years he had repeated recurrences which were treated by cautery-snare removal, roentgen-ray therapy, and gold-filtered radon seeds. A colostomy and perineal resection were then performed. The tumor in the resected specimen was for the most part papillary adenoma with benign structure, but there were areas of colloid carcinoma infiltrating only the superficial portion of the muscle wall. During the five years since operation the patient has remained well, except for repeated inflammatory polyps on the exposed mucosa of the colostomy, and recently the development of a small pedunculated adenoma within the colostomy loop. This was removed; microscopic examination showed no atypical features.

Another patient originally had a tumor 7 cm. in diameter. Biopsy showed a benign papillary structure. Since treatment was refused, the entire tumor could not be studied at that time. Three and one-half years later he returned to the clinic, by which time the tumor had become almost completely annular, and involved the entire rectum from a point just above the mucocutaneous junction to the peritoneal reflection. The lower part, an area almost 7 cm. in diameter, was removed by cautery snare. Examination of multiple sections showed a predominantly benign structure, but there were multiple small foci of in situ carcinoma in the superficial and mid-portions. Three months later the entire

tumor was removed by a limited rectal resection. This tumor measured 12 cm. in diameter (Fig. 17). The area of mucosa from which the tumor had been removed previously was completely covered by recurrent papillary adenoma. Grossly it showed no induration except at the base of the central portion where there was one small, hard nodule, 5 mm. in diameter. This was in the previously treated area. Microscopically it proved to be colloid carcinoma with superficial infiltration of the muscle wall (Fig. 18). The remainder of the specimen was similar to the tissue previously removed.

The last of these eight patients had had a surgical excision with recurrence prior to admission. Our examination of the material previously removed showed one small focus of in situ carcinoma at the base. During the next five and one-half years the patient had six cautery-snare removals and two implantations of gold-filtered radon seeds. All the specimens removed showed uniformly benign structure. He was not examined here again. Subsequently a colostomy was performed elsewhere and he died, presumably of cancer of the rectum, twelve years after he was first seen at Memorial Hospital.

Three patients refused treatment after they were first seen so that their tumors are examples of undisturbed growth. The first of these initially showed superficial foci of carcinoma. After failing appointments for two and one-half years, he returned because of pain and tenesmus caused by an advanced carcinoma; he again refused treatment and died seventeen months later of pneumonia following a fractured hip. The initial biopsy from the second patient showed benign structure except for one minute area of in situ carcinoma in the epithelium of one or two villi (Figs. 14 and 15) together with one or two areas of atypical epithelial proliferation. When the tumor was removed by cautery snare, the specimen showed no other areas of carcinomatous change. Thereafter the patient failed appointments for two years, to return recently with an advanced adenocarcinoma at the site of the original polyp. The third patient showed superficial and deep foci of carcinoma in the original cautery-



FIG. 17. *Papillary adenoma. Gross surgical specimen. The tumor measures 12 cm. in diameter and is the largest of the series. A small area of invasive carcinoma, 5 mm. in diameter, was found at the base in the central portion.*



FIG. 18. *Microscopic view of minute colloid carcinoma found at base of tumor shown in Fig. 19. There is superficial infiltration of the muscular wall.*

snare specimen. A small amount of residual tumor remained after the excision. After failing appointments for a year, the patient returned with an advanced colloid carcinoma. Following an incomplete series of roentgen-ray treatments, he again failed to return; he is still living more than two and one-half years after he was first examined here.

The second pedunculated tumor of the series, completely removed by cautery snare, showed a focus of carcinoma in the base. The patient has been living free of recurrence for fourteen years.

Another patient had the tumor completely removed, in three stages, by the cautery snare; he remained free of recurrence for eleven months but since has failed appointments to date—a period of three years.

The remaining thirteen patients were treated by repeated cautery-snare removals, supplemented by roentgen-ray therapy, radium applicator or gold-filtered radon-seed implantation, or by a combination of all three methods in the same case. Three patients died of carcinoma: One died in fourteen months' time. Another had a single benign recurrence, then went three years without evidence of tumor, but finally died, after five years, with a massive pelvic carcinoma. The third patient showed evidence of liver metastasis in five months, and died of widespread metastases seventeen months after he was first seen.

Three patients died of heart disease: one, with residual tumor in one year; two, after being free of disease for two and one-half and three and one-half years, respectively.

One patient had repeated superficial recurrences over an eight-year period, at the end of which time he died of mesenteric thrombosis. Another did not return after treatment was completed and died seven years later of unknown cause.

One patient had repeated recurrences during a five-year period, seventeen months being the longest period of freedom from disease during this time. Since then—i.e., for the last five years—she has shown no recurrence. The remaining four patients have had repeated recurrences and are living at the present time—one and one-half, two, five

and one-half, and six years after first being seen.

Group 2. The seven patients who had had benign tumors originally and later developed carcinomas in the site of the original polyp had courses of unusual interest. The first was treated by multiple cautery-snare removals, implantation of gold-filtered radon seeds, and roentgen rays. The original tumor showed foci of papillary epithelial hyperplasia. For three years she had repeated recurrences of histologically benign tumor. Two years then elapsed before the next recurrence; on removal, it showed somewhat atypical histological features. She was free of tumor for one year; then developed a recurrence which microscopic examination showed to be adenocarcinoma. On exploratory laparotomy, an extensive colloid carcinoma was found, with widespread metastases in the peritoneum and liver.

The second patient had an initial complete cautery-snare removal of a benign tumor with a few atypical microscopic areas. He failed to return for examination for four years and then was found to have an ulcerating carcinoma at the site of the original polyp. There was no evidence of residual papillary adenoma—the tumor was apparently arising in normal mucosa (Fig. 19). A single-stage, abdominoperineal resection was performed and metastatic nodes were found in the specimen. The patient has remained free of recurrence in the year that has elapsed since the resection.

The third patient had seven excisions and fulgurations with repeated recurrence over an eight-year period prior to his appearance in this hospital. He was treated here by multiple cautery-snare removals, gold-filtered radon seeds, and roentgen rays. The original tumor showed several areas of atypical epithelial changes. There were repeated recurrences of benign structure during the first four and one-half years, when biopsy of a recurrence showed an area of infiltrating colloid carcinoma. After removal of this lesion, there was no further recurrence for three years, when another area of tumor appeared that was found to be entirely benign after cautery-snare removal. Thereafter he showed



FIG. 19. *Adenocarcinoma, in situ in this area. Although occurring at the site of previous removal of a papillary adenoma, it appears to be arising directly from the mucosa. No residual polyp could be found in the surgical specimen.*

no evidence of further recurrence until his death twenty-eight months later—in all, a period of eighteen years after the tumor was first discovered.

The next two patients had a rapid course to death. One of these had two cautery-snare removals during a six-month period. All specimens of the tumor removed were benign; except one that showed a single area of papillary epithelial hyperplasia. Following the second removal, residual tumor remained. The patient disappeared from observation and died three months later. Autopsy showed an extensive rectal carcinoma with metastases to lymph nodes, liver, pleura, and lungs. The other patient had four cautery-snare removals in four months. Again, all but one of the specimens showed benign structure; it had a small, atypical, superficial focus. Obvious infiltration of the anal canal then developed. An exploratory laparotomy was done and multiple liver metastases found. He died two months later, seven months after he was first seen. In retrospect it is reasonable to suspect that infiltrating carcinoma existed in the tumors of both these cases when they

were first seen. However, this could not be determined either by clinical or microscopic examination until the carcinoma was advanced.

The sixth case had repeated cautery-snare removals, and implantation of gold-filtered radon seeds. There were repeated recurrences, one of which showed a superficial area of carcinoma; this followed the second cautery-snare removal four months after the patient's first appearance here. Twenty-one months after admission, a recurrence showed microscopic carcinoma with infiltration of the base. Following this, the tumor infiltrated the anal canal and buttock; the patient died nine months later, two and one-half years after his first appearance.

The last patient of this group had four cautery-snare removals within a ten-month period with recurrence after each. Here, again, only one small area of superficial atypical epithelial change was seen in one specimen. At the end of this time a recurrence showed adenocarcinoma. A two-stage Lahey resection was done. Invasive colloid carcinoma was found arising in the papillary adenoma (Figs. 20 and 21) and metastases to nodes. The patient died postoperatively. Autopsy revealed liver metastases. An incidental finding was an early Brenner tumor of the ovary.

Group 3. The tumors in this group of cases showed no deviation from uniformly benign structure. A cautery-snare removal with suture ligation of the base was done in one patient with a tumor 3 cm. in diameter. He remained free of recurrence more than five years, and was discharged from further follow-up. Another patient with a comparatively small tumor, 4 cm. in diameter, had an endotherm excision; the tumor has not reappeared for six years. Two other patients had small tumors: One, 3 cm. in diameter, was removed in two operations by cautery snare followed by roentgen-ray and radium-applicator treatments, and has not recurred in one year's time. The other, 4 cm. in diameter, was removed in one stage by cautery snare; six months later a recurrence was removed with biopsy forceps; at the time of writing the patient has had no further recur-



FIG. 20. *Invasive carcinoma arising in a papillary adenoma. Note the sharp juncture between benign polyp and carcinoma.*



FIG. 21. *Same case as Fig. 20. Transition from structure of adenocarcinoma to colloid carcinoma.*

rence, a period of more than three years.

One patient had two cautery-snare removals, was reported free of tumor two and one-half years later by her local physician, and has not returned. Another had three cautery-snare removals and roentgen-ray treatments over a seventeen-month period. He then remained free of recurrence until his death following cholecystectomy seven years later.

The last four patients have run courses of considerable interest. The first had a partial cautery-snare removal of a large tumor. A fractured hip prevented her return for two years. The lesion was still benign, was removed by cautery snare, and has not recurred in one and one-half years. Another patient had four cautery-snare removals, with recurrence, during a fourteen-month period. She was free of recurrence for three years, after which time another cautery-snare removal was performed. Sixteen months later a further benign recurrence was similarly removed, followed by radium-applicator treatments. She has remained free of tumor for eight and one-half years. The next patient

had the original papillary adenoma removed by cautery snare followed by radium-applicator treatments. After two recurrences at yearly intervals, she remained free of disease for six years when another recurrence ensued. This has only recently been removed. Microscopic examination still shows benign structure throughout.

The last patient originally had an almost annular tumor that was removed by the cautery snare. Seventeen months later a recurrence was fulgurated. The patient then developed a marked inflammatory stricture of the rectum for which a limited resection was recently performed—five months after the fulguration. In the resected specimen, an area of recurrent papilloma, 2.5 cm. in diameter, was found above the stricture. There was no area of carcinomatous change. Nearby there was a small, puckered, ulcerated area 6 mm. in diameter, the base of which was formed of granulation tissue. Attached to one margin was a minute area of benign papilloma.

Group 4. Originally two patients in this group had benign tumors but were not seen

TABLE 3
CLINICAL COURSE

Treatment	Dead					Living						
	Ca.	Prob. ca.	Other cause with invas. ca.	Other cause—no benign evid. recurr.	Status un-known	Another prim. ca. of colon	Total	No evid. recurr.	With invas. ca. recurr.	With benign un-known Status	Total	Grand Total
<i>In Situ Carcinoma in Original Tumor</i>												
Local surgical excision	—	—	—	—	—	—	0	2	—	—	2	2
Perineal resection and colostomy	—	—	—	1	—	—	1	1	—	—	1	2
Abdominoperineal resection	1	—	—	—	—	—	1	1	—	—	1	2
Limited rectal resection	—	—	—	—	—	—	0	1	—	—	1	1
Cautery-snare removal (single and mult.)	—	—	1	—	—	—	1	1	—	—	1	2
Cautery-snare removal and irradiation.	3	1	—	1	1	—	8	1	2	1	6	14
Incomplete or no treatment	—	—	1	—	—	—	1	—	2	—	2	3
TOTALS	4	1	2	1	1	0	12	7	4	1	14	26
<i>Original Tumor Benign</i>												
Local surgical excision	—	—	—	—	—	—	0	2	—	—	2	2
Abdominoperineal resection	—	—	—	—	—	—	0	1	—	—	1	1
Limited rectal resection	—	—	—	—	—	—	0	1	—	—	1	1
Lahey resection	—	—	1*	—	—	—	1	—	—	—	0	1
Cautery-snare removal (single and mult.)	—	—	—	—	—	2	2	1	—	2	3	5
Cautery-snare removal and irradiation.	4	—	1	2	1	—	8	3	—	1	4	12
TOTALS	4	0	2	0	1	2	11	8	0	1	11	22
GRAND TOTAL	8	1	4	1	2	2	23	15	4	2	25	48

* Postoperative death.

again following removal of the polyp. One had two cautery-snare removals and roentgen-ray treatments. He failed to return and died two years later of unknown cause. The other had a cautery-snare removal one and one-half years ago.

Two patients died of carcinoma of the colon: in the sigmoid in one; in the descending colon in the other. In each case this co-existed with, but was not discovered until after removal of, the papillary adenoma.

Initially, the last patient had four cautery-snare removals, gold-filtered radon-seed implantation, and roentgen-ray therapy over a four-month period. She was free of disease for six years, then an area of induration appeared. Repeated biopsies showed recurrent polyp with somewhat atypical microscopic foci but no definite carcinoma. She died several months later at another hospital from a urinary infection. At autopsy the treated area was interpreted as being a carcinoma limited to the muscular coat of the rectum with a localized abscess at the site of radon-seed implantation. There were no metastases. Two small adenomas were found in the rectum and descending colon.

Summary. Table 3, summarizing the clinical course of the series, shows that there is little difference in prognosis between those who originally showed carcinomatous change and those in whom it appeared subsequently. In the latter group, the carcinoma appeared from four months to six years after the patient was first seen in this hospital, and in one case twelve and one-half years after the tumor was first treated elsewhere.

Fifteen of the total group (31.2 per cent) are living without evidence of tumor from a few months to sixteen years after the last recurrence. Five additional patients died of other cause after being free of recurrence for two to seven years. Eight (16.6 per cent) died of carcinoma that developed at the site of the polyp nine months to seven years after the patient was first seen. Another died after twelve years, presumably of the same cause. Four patients, with carcinoma, are living two to five years after they were first seen.

All but two of the patients treated by local or radical surgical resection are living free of

tumor recurrence. Of these two, one had lymphatic invasion at the time of operation and died of metastases; the other died post-operatively.

The results of cautery-snare removal with or without irradiation are variable. Of thirty-three patients treated by this method alone, six are living free of recurrence. An additional four died of other cause without evidence of local tumor recurrence.

RELATION OF MICROSCOPIC STRUCTURAL VARIATION TO CLINICAL BEHAVIOR

The only section of the detailed microscopic study of papillary adenomas that yielded significant findings was that of the epithelial component of the glands and villi. Two facts became evident: First, carcinomatous change was always accompanied or preceded by atypical epithelial changes, which never appeared to any significant degree in the polyps that remained benign, even when these recurred repeatedly over a period of years. Second, no gradual or uniform chronological transition from benign to malignant structure was demonstrable.

The atypical changes consist of papillary tufting of the cells covering the surface of the villi and lining the lumina of the glands, accompanied by secondary lumen formation within the glands without interposition of a basement membrane between the separate lumina. This papillary tufting presumably is evidence of rapid growth on the part of the surface cells, causing them to become bunched together, to be dragged out from the basement membrane, and to project above the surface of adjacent cells. The tufting varies from a sharply demarcated exfoliative type to a more gradual wavy pattern and is generally associated with complementary epithelial infolding into the substance of the villus or stalk (Figs. 22 to 26). These changes occurred in any portion of the polyp—periphery, central portion, or base. In some instances the change was limited to a single arborization, in others it appeared in several. In no case did it occur diffusely throughout the tumor, but always focally with intervening areas of benign structure.

As previously stated, although the appear-



FIG. 22. *Very early atypical change, showing a slight degree of papillary tufting of epithelial cells in a papillary adenoma.*



FIG. 23. *Very early atypical change, showing infolding of surface epithelial cells of a villus in a papillary adenoma.*



FIGS. 24 and 25. *Different areas in same block. Advanced atypical epithelial change in a papillary adenoma. Marked papillary tufting and secondary lumen formation, without loss of nuclear or cellular polarity.*



FIG. 26. *Advanced atypical epithelial change in a papillary adenoma. Marked glandular proliferation, infolding, and secondary lumen formation. Here again nuclear and cellular polarity are still maintained.*

ance of this change in epithelial architecture was always accompanied or followed by carcinoma, no uniform, gradual progression in degree of abnormality could be traced to frank carcinomatous change. In other words, there was no chronological, orderly transition of the tumor as a whole from benign structure through increasing degrees of epithelial abnormality to a culmination in metastasizing carcinoma. The change was purely focal and the sequence of events so variable that the time and extent of malignant transformation could not be predicted. As shown in the previous section, the changes were sometimes noted in an early specimen: months or years of repeated recurrence of structurally benign polyps followed; later an abrupt change to fully malignant, invasive, and metastasizing carcinoma occurred. Others initially showed microscopic areas of carcinoma with atypical changes elsewhere in the polyp, and never developed infiltrative qualities. Again, atypical changes were noted constantly over a long period of time, ending at last in clinical car-

cinoma. Finally, in still others, these changes were immediately followed by rapid, clinically malignant transformation and metastasis.

While some cases that initially showed foci of carcinomatous change later had recurrence of a benign nature and did not progress to clinically invasive carcinoma, *no tumor that showed a uniformly benign structure originally and in the early recurrences has developed infiltrating carcinoma to date.*

Like the amount of mucus secretion, the number of mitoses had no relation to change in the character of the epithelial cells nor to the development of carcinoma. This was also true of capillary engorgement, hemorrhage, and edema of the villi. This edema, sometimes marked, is well shown in Fig. 27.

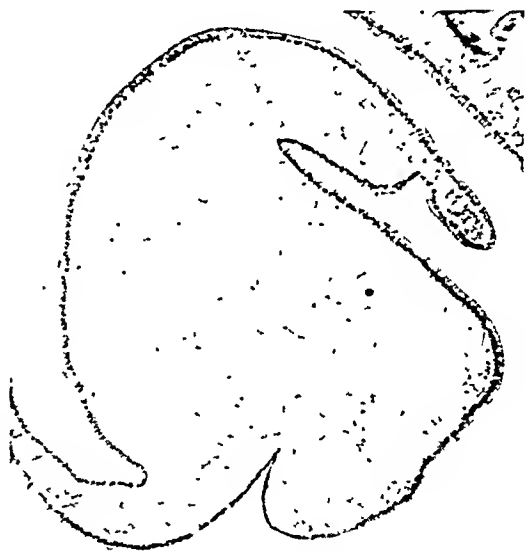


FIG. 27. *Marked edema of a villus in a papillary adenoma.*

Interstitial inflammatory cell infiltration of villi and stalk was seen in varying degree in almost all of the tumors. Plasma cells and lymphocytes usually predominated, with fewer eosinophils and neutrophils. Numerous macrophages were seen in the villi in one case. There was no correlation between the degree or type of inflammatory exudate and carcinomatous transformation. Enlargement and distortion of the glands were likewise seen in all tumors studied, regardless of the presence or absence of malignant change.

The comparative study of the nine rectal adenocarcinomas that showed residual portions of benign papillary adenoma revealed foci of epithelial change in these residual benign portions similar to that described in the first part of this section. In all cases the carcinoma had invaded the polyp to such an extent that its point of origin could not be determined. The average age of these patients was 67.2 years, a little more than four years older than the average age of the patients with papillary adenomas.

SUMMARY AND CONCLUSIONS

Papillary adenomas or villous tumors can be considered to be a growth variant of the common mucosal adenoma, characterized by (1) disproportionately increased growth of the surface epithelium in comparison to the growth of the epithelium of the glands; (2) marked tendency to recur after local removal, and (3) lateral spread by replacement of the covering epithelium of the surrounding mucosa. Although they show a different method of growth, there is no evidence that their mode of origin is different from that of other adenomas. They occur in an older age group than do most adenomas, in an even older age group than carcinomas, and characteristically they reach large size. The attachment to the bowel wall is primarily flat, with areas of pedunculation occurring within the tumor itself. The tumors generally evidence slow, steady growth and apparently a direct relation between size and duration of symptoms. Most commonly they are found in the rectum and are generally solitary and unassociated with other colonic or rectal tumors. Their outstanding clinical characteristic is the tendency to repeated recurrence after removal. In comparison with adenocarcinomas and other adenomas, they are rare.

In this series 68.7 per cent of the papillary adenomas showed areas of cytological carcinoma either in the original tumor or in a recurrence at the site of removal; 39.5 per cent developed invasive carcinoma.

When carcinoma occurs, it may appear in any part of the papillary adenoma; it shows no special predilection for surface or base.

Induration and surface ulceration are generally reliable evidence of malignant transformation, but their absence does not guarantee benignity.

The proportion of colloid carcinoma is higher in the carcinomas arising in papillary adenomas than in the group of rectal carcinomas as a whole.

The microscopic observations of this study indicate that those tumors that show atypical epithelial changes, as evidenced by papillary tufting and infolding of the surface and glandular cells, concomitantly or subsequently develop areas of microscopic carcinoma. This, however, is no indication of the probable occurrence or rapidity of invasion. Conversely, no tumor that has not shown a significant degree of epithelial abnormality, either in its original form or in early recurrences, has yet developed carcinoma in spite of repeated recurrence over a period of years.

Although there is no evidence that the papillary adenoma has a mode of origin different from that of other adenomas, yet, because of its method of growth, clinical incidence, and behavior, there is ample justification to regard it as an entity. To quote Kolodny: "It is obvious that the single criterion of whether a certain peculiarity in a group of tumors is to be sufficient reason for an exclusion of the group in a separate variety or type is whether or not this peculiarity influences the clinical course of the tumors." Clinically, this type of tumor occupies a position midway between a benign adenoma and an adenocarcinoma. Although more than half the cases in this series showed areas of *in situ* carcinoma initially, there were no more deaths from carcinoma among these patients than among those whose original tumor showed only atypical change. The clinical course varies considerably from the extreme of rapidly progressing carcinoma to that of a completely benign tumor—with all stages in between.

It is difficult to argue with those who maintain that those tumors that subsequently develop infiltrative properties must have been carcinomatous from the beginning rather than examples of malignant change in an originally benign tumor. Since it was

impossible to do serial sections on these tumors, no absolute conclusion can be drawn. Let it suffice, that the behavior of the group as a whole is not that of primary carcinoma. If a papillary adenoma is soft to palpation and shows only atypical epithelial change, there is then no other morphological or clinical criterion by which one can determine whether it will behave as an invasive carcinoma or as a benign tumor. Furthermore, it would be unreasonable to maintain that a tumor that was carcinoma from the beginning would recur superficially at irregular intervals over a six-year period, and then suddenly invade, metastasize, and cause death.

Because of the peculiar clinical behavior of this type of adenoma, and its evident malignant potentiality, it is suggested that all those tumors that show atypical epithelial structure and cannot be fully removed by local surgical excision, be removed by resection of the rectum. Since metastases have not been demonstrated in any case prior to invasion of the bowel wall, a somewhat limited surgical procedure may suffice. Repeated cautery-snare removal or fulguration is not adequate to eradicate most cases and should be reserved for those tumors of entirely benign structure occurring in patients who can be kept under close observation.

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THE DIAGNOSIS OF BRONCHOGENIC CARCINOMA BY SMEARS OF BRONCHOSCOPIC ASPIRATIONS†

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BRONCHOGENIC carcinoma ranks second only to cancer of the stomach as a cause of death in males in the cancer age group. An estimated 8000 new cases of carcinoma of the lung occur in the United States alone each year, and there appears to be an increase in the incidence of this tumor. The problem becomes the more acute when it is realized that the five-year salvage ranges between 5 and 8 per cent, even when the best surgical treatment is available. Recently, Ochsner, DeBakey, and Dixon analyzed the available statistics and reported that of every twenty-five cases of bronchogenic carcinoma seen clinically by the thoracic surgeon, fifteen patients are explored; in nine the tumor is resectable but of these nine resected, only two (20 per cent) survive for five years or more. Correction of this discouraging situation requires earlier extirpative surgery and earlier surgery depends upon earlier diagnosis.

The public, the family physician, and the consultants must all contribute to the early diagnosis of bronchogenic carcinoma. Mass education must render the layman as alert to the possible significance of a persistent cough, particularly if accompanied by hemoptysis, as is the average woman to the discovery of a lump in her breast. The physician first consulted must exclude carcinoma of the lung by the ordinary available diagnostic means, such as roentgenography and bronchoscopy. Finally, the consulting thoracic surgeon, internist, roentgenologist, and pathologist must constantly improve their diagnostic techniques.

The difficulty of clinical diagnosis of cancer of the lung is well known. The differen-

tial diagnosis may be complex. For instance, a satisfactory biopsy specimen can be obtained through the bronchoscope in only one-half of the tumors encountered in this hospital. True, there are indirect signs of primary pulmonary tumors such as widening of the carina, fixation of a bronchus, and evidence of extrinsic pressure, but these signs are too frequently associated with inoperable tumors. Conversely, with the thorax open at exploratory operation, it may be impossible to determine the nature of an intrapulmonary mass even by palpation; and direct biopsy may be unsafe owing to associated suppurative processes or impossible because of the size or location of the neoplasm.

As clinicians appreciate, after a primary carcinoma of the lung obstructs a bronchus, the suppurative process beyond the tumor may present the picture of pneumonia, lung abscess, or empyema.

There are, then, *three* diagnostic zones: at one pole, the established diagnosis; at the opposite pole, the inflammatory lesion not associated with neoplasm; in either of these two zones, the clinician can make his recommendations for surgical or medical treatment with confidence. Between the clearly neoplastic and the clearly inflammatory groups of cases, lies the twilight zone of the *presumptive diagnosis*; here lurk the specter of *unnecessary resection* and the tragedy of *lost opportunity*.

Smears of bronchial secretions stained by the Papanicolaou method offer further possible clarification in the zone of the presumptive diagnosis. This enables more patients to have the advantages of earlier surgery, without the delays and dangers of tissue diagnosis at the time of thoracotomy. The method makes possible the diagnosis of tumor beyond the range of vision of the bronchoscope, including neoplasms situated in the upper lobes,

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† This investigation was aided by a grant from the American Cancer Society.

Received for publication, February 18, 1948.

peripherally, or beyond stem bronchi and their major subdivisions.

Herbut and Clerf have reported very favorable results in which this technique was used with an accuracy of 73 per cent in cases of carcinoma. They chose to study bronchoscopic aspirations in preference to sputum because of the factor of dilution, and because several reports in the literature concerning the usefulness of sputum examination for tumor cells were not encouraging.

There is no question but that the problem would be simplified if sputum could be used so that it would not be necessary to resort to the bronchoscope for secretions. The ease of collecting the specimen and the possibility of its use as a screening test would be of great practical value. There are, however, disadvantages in the use of sputum. Aside from the fact that it is a more dilute specimen of tumor cells, the sputum specimen contains numerous cells from the mouth and pharynx that must also be differentiated from the cancer cells. This particular problem is simplified in the cellular pattern of the bronchial smears. Finally, sputum truly coughed up would obviate many of these objections, but unfortunately the patient with early and resectable bronchogenic carcinoma frequently does not have a productive cough. Generally, it is an irritating, harsh, paroxysmal, unproductive cough. A productive cough in bronchogenic carcinoma usually implies obstruction of a bronchus with atelectasis and supuration of the involved lobe or lobar segment.

Despite these acknowledged difficulties in the examination of sputum, Papanicolaou³ has recently reported favorable results with its use. His experience covered fifty-four cases with positive smears in twenty-two; eighteen were proved pathologically and four clinically. In seven, the smear was suspicious because of atypical cells; six of these patients later proved to have carcinoma. In the remaining twenty-five cases with negative smears, three proved to be carcinoma, in one the diagnosis was in doubt, and the remainder proved to be negative.

In short, the collection of a concentrated specimen by direct aspiration of the bronchial

zone just proximal to the tumor, or of the drainage pathway of the suspected parenchyma, would seem to offer the optimal specimen for smear examination. For these reasons, bronchoscopic aspirations stained by the Papanicolaou method were used for this study, the purpose of which was to determine the usefulness of the bronchial smear in the diagnosis of primary pulmonary carcinoma. To do so it was felt that answers to the following questions would determine the usefulness of this technique:

1. How precise are the criteria for distinguishing cancer cells from normal cells?
2. In how many cases of tumor will the smear be positive and in how many will it be negative?
3. Will the smear ever be positive in cases with inflammatory (benign) lesions?
4. Will the smear technique make possible the diagnosis in cases of peripheral and upper lobe tumors from which biopsy specimens cannot be taken through the bronchoscope?

MATERIALS AND METHODS

A preliminary study was made of bronchial secretions collected at thirty-five autopsies including six cases of bronchogenic carcinoma and four cases of metastatic carcinoma; the others had no demonstrable tumor. With organs *in situ*, secretions were aspirated from the bronchial pathway just proximal to the known tumor or were collected from the right and left main-stem bronchi where there was metastatic carcinoma or no carcinoma. These thirty-five cases were treated as known negatives and known positives and served to establish both the normal and abnormal cytology of the bronchial secretions.

Specimens were obtained at bronchoscopy from 170 patients. At the start of this study, the Clerf aspirator with a glass collecting cup was used. In many cases a very small amount of secretion was obtainable so that it was necessary to drain a little saline through the aspirator to collect the specimen. This invariably resulted in an unsatisfactory degree of dilution and occasionally in damage to cell outlines and characteristics. This method of collection is now limited, therefore, to patients with copious secretions.

An aspirator was next devised from a 60 cm., end-on, bronchoscopic aspirating tube to which was attached a piece of No. 12 catheter, lightly plugged with cotton. It has proved very satisfactory, particularly in patients with scant secretion. This has now been modified into the type of collector shown in Fig. 1. An ordinary end-on bronchoscopic aspirating tube with a detachable tip $1\frac{1}{2}$ inches from the end is used. The tip is un-

formed and the suspected area carefully examined. Tracheal and occasionally main-stem bronchial secretions are aspirated and discarded. The tumor, or bronchus of the lobar segment involved, is visualized if possible, the specimen suction tip inserted, and the area aspirated. If the tumor is visible, a biopsy specimen is then taken. In most of the cases, four smears are made from each patient. When the secretions are scanty, only two may

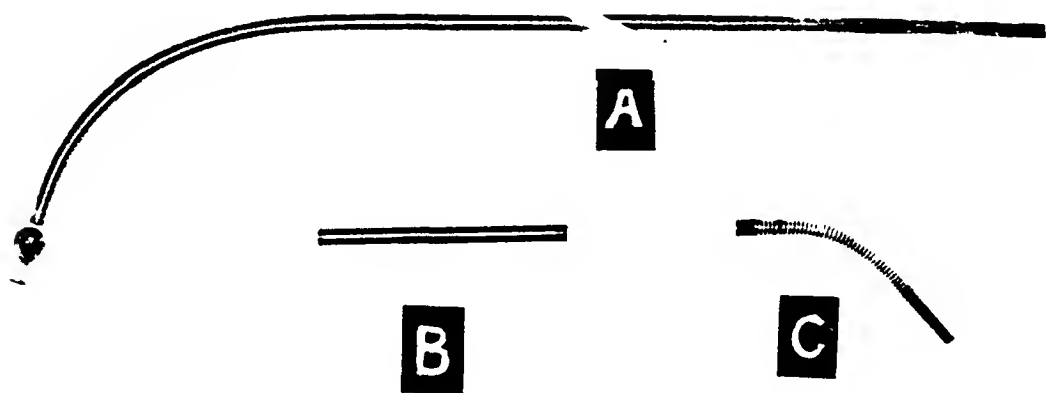


FIG. 1. Photograph of collector: (A) end-on bronchoscopic aspiration tube; (B) detachable straight tip containing cross-bar into which a plug of cotton is placed; (C) flexible curved tip for aspirating upper lobe bronchi.

(This instrument is available at the George P. Pilling & Son Co., 3451 Walnut Street, Philadelphia 4, Pa.)

screwed and cotton lightly packed in the lumen against a thin crossbar. The secretions are caught on the cotton plug. Following aspiration, the tip is unscrewed and the cotton plug pushed out, carrying all secretions with it; this is smeared directly on slides which are placed immediately in the alcohol-ether fixative. If a patient has no apparent secretion, 1 to 2 cc. of saline may be injected into the suspected bronchus and a specimen taken in the same manner. This obviates the dispersion of a scanty specimen along the walls of the aspirator before it reaches a collection cup. If the tumor is central, a straight tip is used; if one of the upper lobes is suspected, the curved flexible tip is attached and inserted directly into the suspected orifice and a specimen taken.

In the routine case, bronchoscopy is per-

formed and the suspected area carefully examined. Tracheal and occasionally main-stem bronchial secretions are aspirated and discarded. The tumor, or bronchus of the lobar segment involved, is visualized if possible, the specimen suction tip inserted, and the area aspirated. If the tumor is visible, a biopsy specimen is then taken. In most of the cases, four smears are made from each patient. When the secretions are scanty, only two may

be made, but on occasion as many as ten have been prepared from one patient. The smears are stained by the Papanicolaou method as described by Papanicolaou and Traut. They are read and the diagnosis reported with no prior knowledge of the clinical findings. The entire surface area of the four slides in each case is examined with the medium-power objective of the microscope. The high, dry objective is used when any suspicious cells are seen under the medium-power. A smear is reported as negative when no cancer cells are found after a 30-minute search of the four slides.

PATHOLOGY

Macroscopic Appearance. In this series, the macroscopic appearance of the bronchial secretions was of no aid in diagnosis. Herbut

and Clerf call attention to the presence of blood in the secretions in cases of cancer. They found that the secretions were grossly bloody or were streaked with bright blood or

were stained brown by changed blood. This was true in our study, but it was likewise true that numerous inflammatory conditions, particularly bronchiectasis, gave rise to blood-

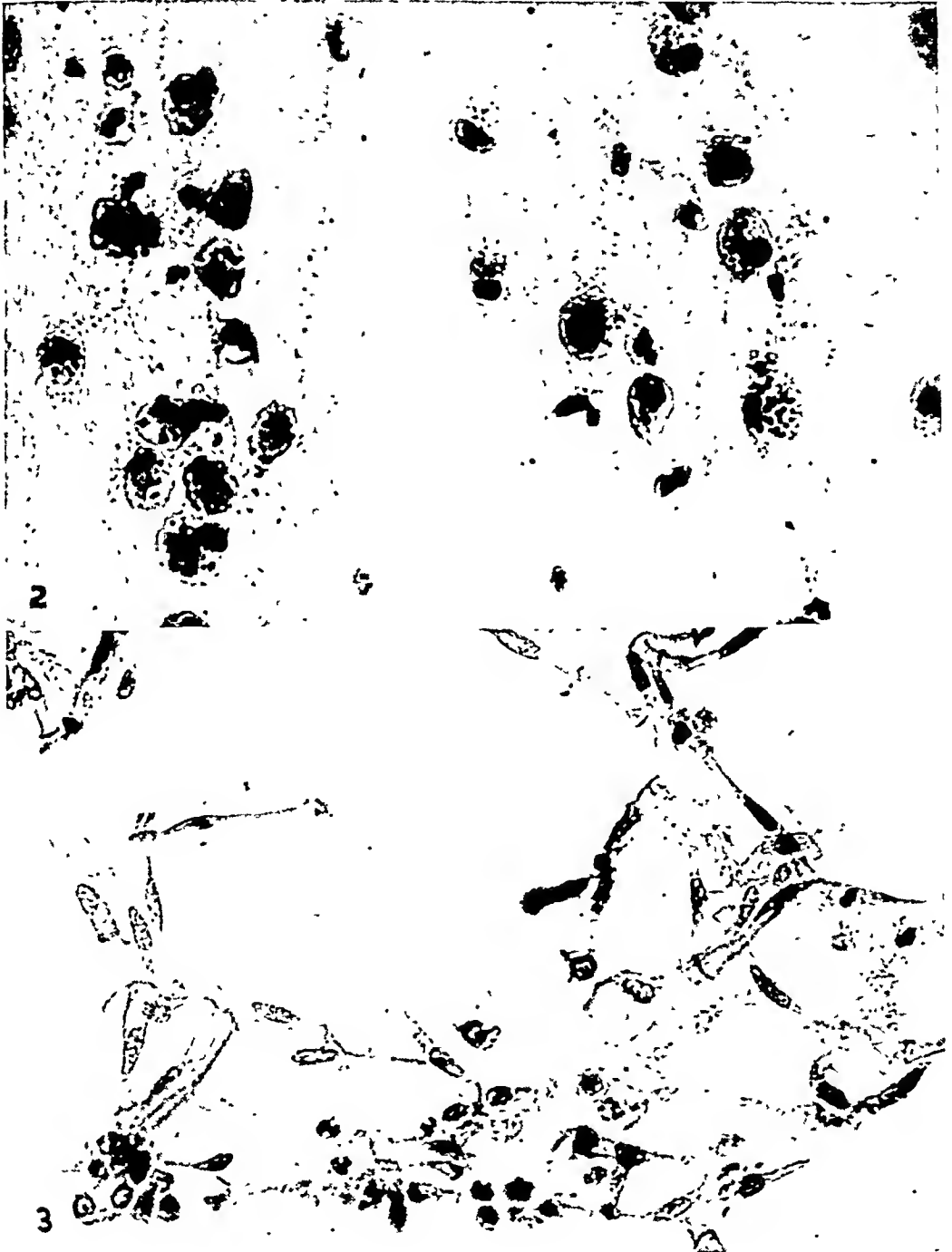


FIG. 2. *Macrophages showing carbon particles in the cytoplasm ($\times 800$).*

FIG. 3. *Ciliated columnar cells from the tracheal and bronchial mucosa ($\times 800$).*

streaked or rusty secretions. Microscopically almost every case showed evidence of blood, usually in the form of red blood cells. In general, we found no correlation between the gross appearance of the secretions and the presence of carcinoma.

Normal Cells. Every properly prepared smear contains numerous cells derived from the alveolar spaces and from the mucosal lining of the trachea and bronchi. The six types most commonly seen are leukocytes (polymorphonuclear and lymphocytic), plasma cells, red blood cells, ciliated columnar epithelial cells, nonciliated cuboidal cells, and macrophages. These are present in almost every smear.

The polymorphonuclear leukocytes are readily recognized as small cells with multilobulated nuclei and a pale green or pink cytoplasm. The lymphocytes are smaller and have a dark-staining round nucleus and a small amount of cytoplasm that varies in its staining properties. Plasma cells have the same appearance as plasma cells in tissue—an eccentric nucleus and peripheral clumping of the nuclear chromatin.

Macrophages are often present in large numbers (Fig. 2). These cells are somewhat larger than polymorphonuclear leukocytes, have a round or ovoid shape, and usually, an eccentrically located ovoid nucleus. The chromatin of the nucleus is finely dispersed. They are easily recognized when the cytoplasm contains large carbon particles or golden-brown pigment. Many, however, have a pale green or pink cytoplasm with no phagocytized debris.

Ciliated columnar epithelial cells derived from the tracheal and bronchial mucosa are present in almost every smear. The base of these cells tapers to a sharp point and the distal end is usually flat and covered with cilia (Fig. 3). The nucleus is most often elongated and ovoid with finely stippled chromatin. Occasionally these cells are seen in groups and are oriented in the same manner as in the intact bronchial mucosa. Scattered among the ciliated cells are numerous goblet cells which are more prominent in some smears than in others.

Nonciliated cuboidal cells usually occur in small groups (Fig. 4). The nuclei are round, of uniform size, and contain finely stippled chromatin. The cytoplasm frequently stains green and is scant in amount. However, the cytoplasmic stain is not constant and many cuboidal cells have pink or orange cytoplasm. Herbut and Clerf have described these cells and designated them as "intermediary cells." Although it cannot be definitely proved, it is probable that they represent the nonciliated cuboidal cells of the respiratory bronchiole. Such cells may be seen in any microscopic section of lung and correspond in appearance to the cuboidal cells in the smear.

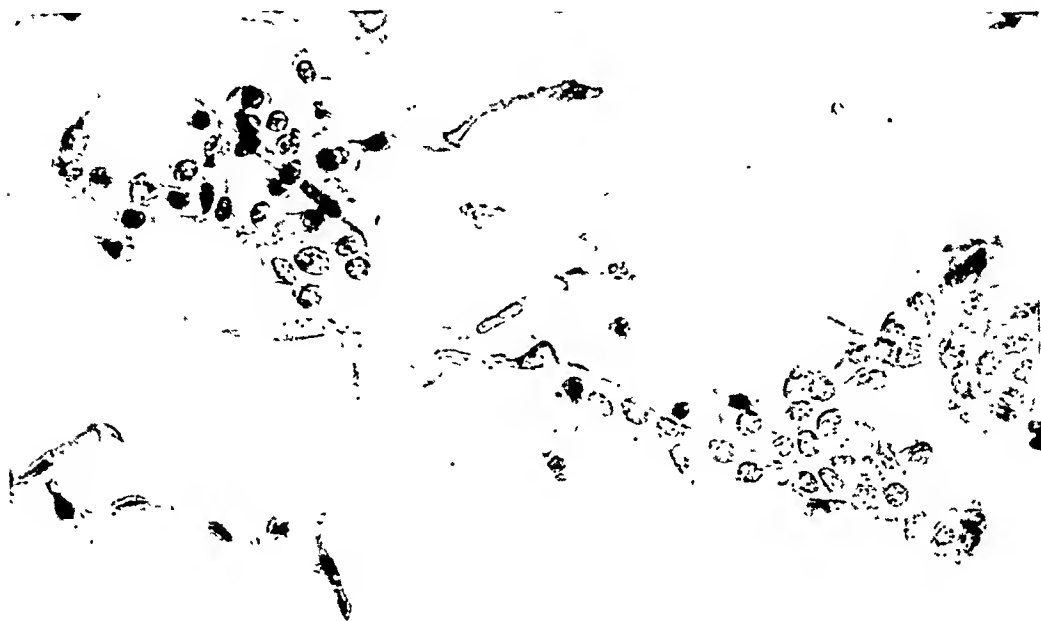
Squamous cells are infrequently seen. They are large, wafer-like cells with angular, irregular cytoplasmic edges and small, round, central nuclei (Fig. 5). They are found singly or in groups, and in most instances in this series were not associated with cancer cells when they were few in number. However, increased numbers of "pavement" cells were seen in smears from cases of epidermoid carcinoma. It is probable that some of the "pavement" cells are derived from the stratified epithelium of the buccal mucosa and pharynx and are aspirated into the bronchial tree. Some are undoubtedly derived from the well-differentiated portion of epidermoid carcinoma. Herbut and Clerf found them to be associated with squamous-cell carcinoma rather frequently.

Cancer Cells. There are several general characteristics that serve as a guide to the recognition of cancer cells. The cytoplasm is often scant in amount and stains either blue, red, orange, or green. The cytoplasmic characteristics are variable and of little aid in tumor-cell recognition.

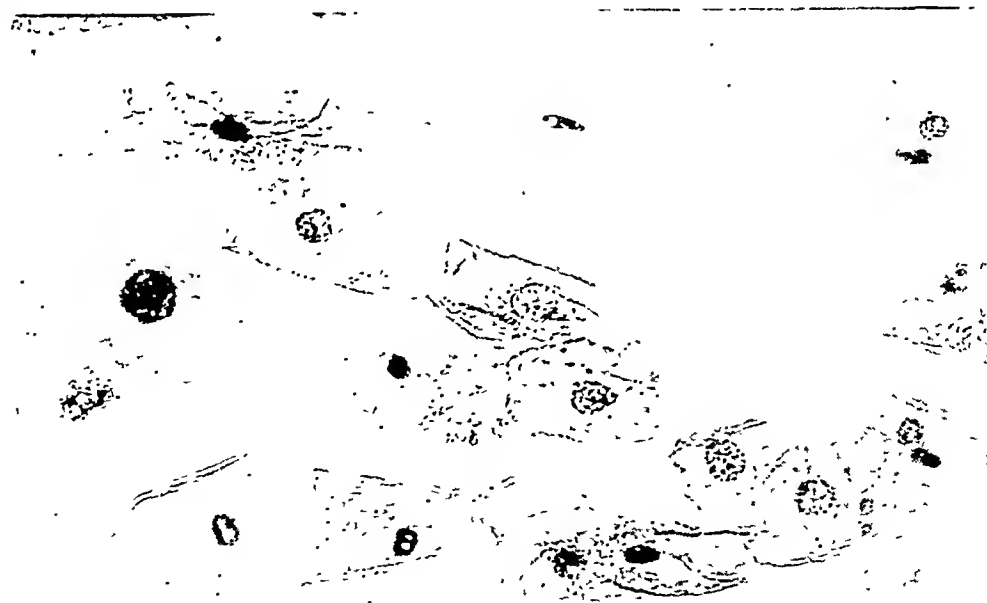
It is probably safe to say that the recognition of tumor cells is based almost entirely upon the nuclear changes. The nuclei are large in proportion to the amount of cytoplasm and vary greatly in size and shape, best demonstrated when the cells occur in small groups. They are hyperchromatic; in some instances the nucleus is a solid purple mass with no visible intranuclear detail. In some cells the chromatin is clumped together in

coarse granules rather than having a finely stippled distribution. The nucleoli of the tumor cells are frequently large and prominent.

Mitotic figures are very rarely encountered. In this study only two were found in the examination of 816 smears. One (Fig. 6) was found in a case of organizing pneumonia with



4



5

FIG. 4. Two groups of nonciliated cuboidal cells probably derived from respiratory bronchioles. A few ciliated columnar cells are also present. ($\times 800$.)

FIG. 5. Group of "pavement" cells probably derived from the buccal mucosa and aspirated into the bronchi. ($\times 800$.)

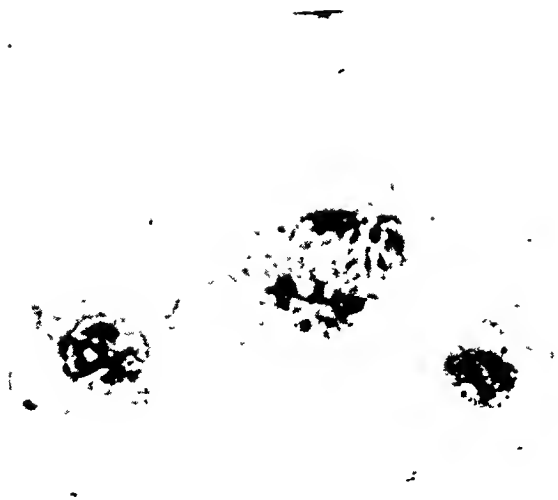


FIG. 6. Mitotic figure from a case of organizing pneumonia ($\times 800$).

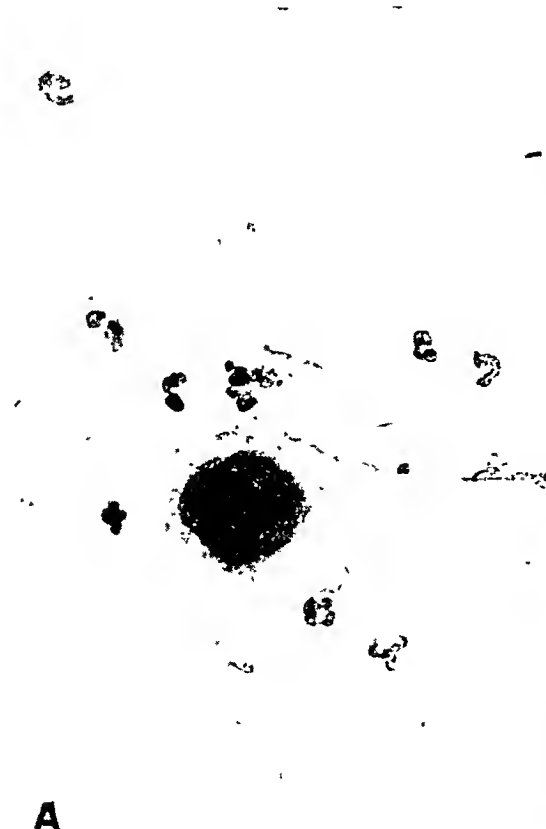


FIG. 7. Mitotic figure from a case of bronchogenic carcinoma ($\times 800$).

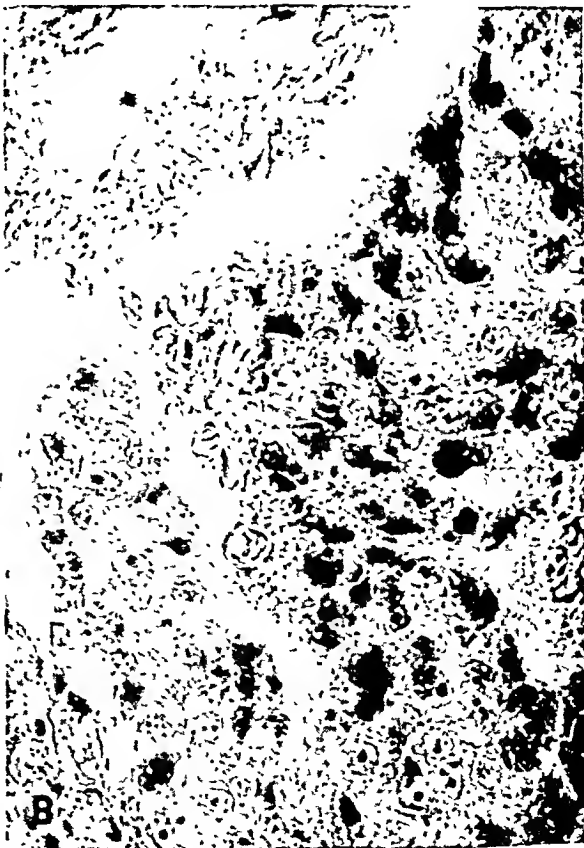
no demonstrable evidence of tumor. The other occurred in a case of far advanced cancer (Fig. 7). Papanicolaou and Traut have discussed the rarity of mitotic figures in vaginal smears and point out that since the

cells in the secretions are dead, desquamated cells derived from the surface of the tumor, it is understandable that mitotic figures are so rare.

Whenever possible, the microscopic ap-



A



B

FIG. 8. A, Typical tumor cell showing hyperchromatism, large nucleus, scant cytoplasm. B, Squamous-cell carcinoma of bronchus. Same case as A. Note cells near surface with hyperchromatic nuclei. ($\times 800$.)

pearance of the tumor tissue was compared with the cells found in the smear. The close correspondence between the cytology of both tissue and smear was striking. The cell pictured in Fig. 8A is a characteristic tumor cell. The whole cell is larger than any normal one.

The nucleus is hyperchromatic with wrinkled edges and the cytoplasm is relatively scanty. When this cell is compared with a section of tissue from the same patient (Fig. 8B), it can be seen that cells of the same description are in the process of desquamation near the sur-

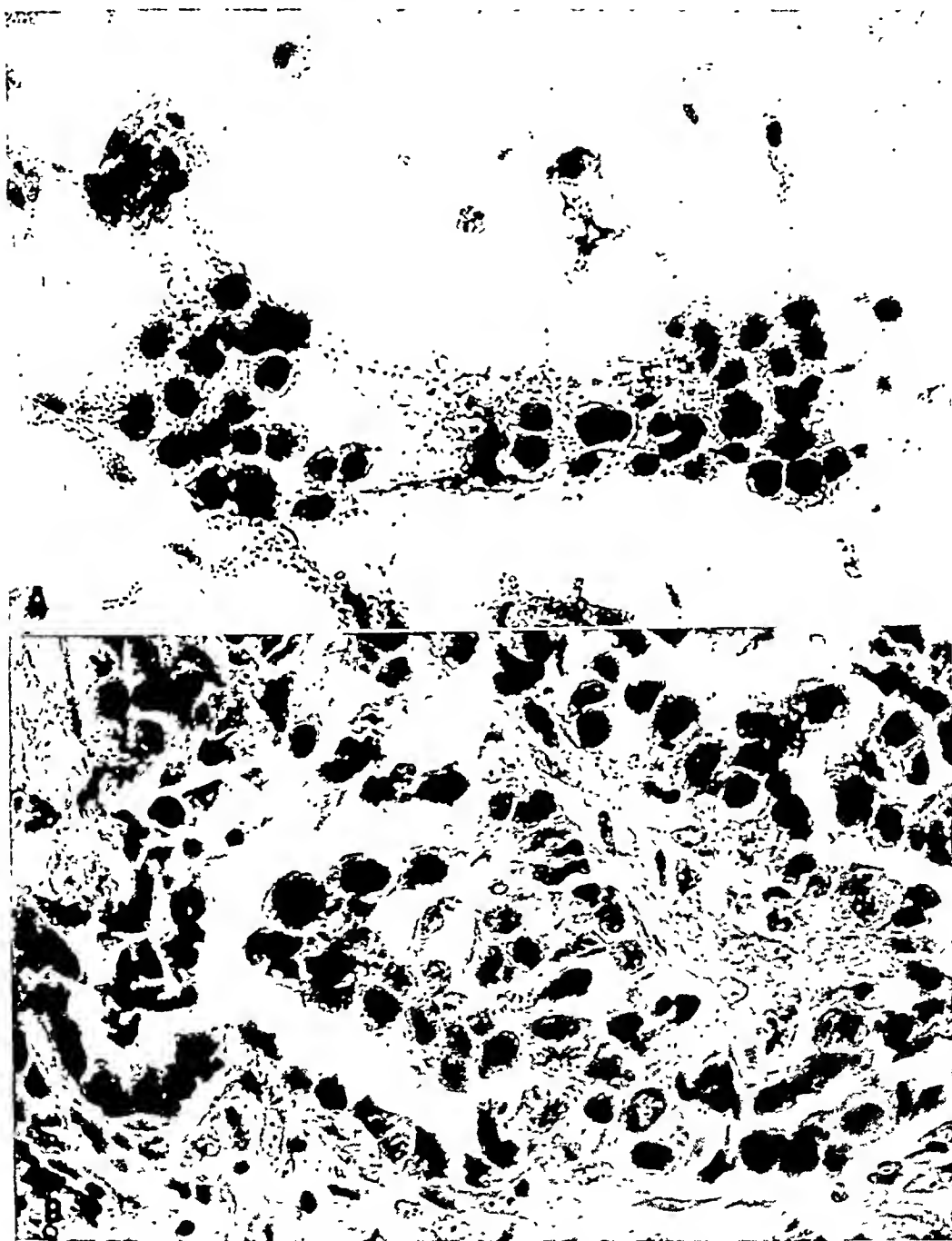


FIG. 9. A, Group of tumor cells demonstrating hyperchromatism and variation in size and shape of nuclei. B, Tissue from same case as A. Note similarity of the cells in tissue and in smear. ($\times 800$.)

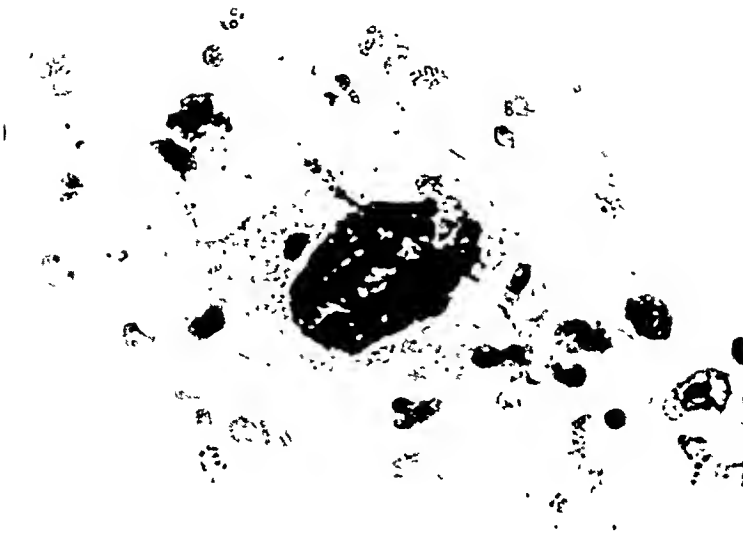


FIG. 10. A, *Giant-sized tumor cell from smear. Note hyperchromatism and wrinkled nuclear edge. ($\times 800$.)*

face of the tumor. However, the cells in the tissue are smaller than the cells in the smear—a phenomenon seen frequently when tissue and smear are compared. Since the photomicrographs were all taken at the same mag-

nification, the difference in cell size is a real one.

A group of tumor cells demonstrating several features of diagnostic importance appears in Fig. 9A. The nuclei are hyperchro-



FIG 10. B, *Tissue from same case as A. Epidermoid carcinoma. ($\times 800$.)*

matic, vary in size and shape, and are relatively large in proportion to the amount of cytoplasm. Comparison with Fig. 9B shows the close correspondence of these cells with the groups of cells in the section of tissue from the same patient.

Sometimes bizarre giant-sized tumor cells,

such as the one in Fig. 10A, are encountered. This cell demonstrates the irregular edge of the nucleus which is a frequent finding in tumor cells. Figure 10B shows a section of tissue from this patient in which the same hyperchromatic, irregular, wrinkled nuclei are present.

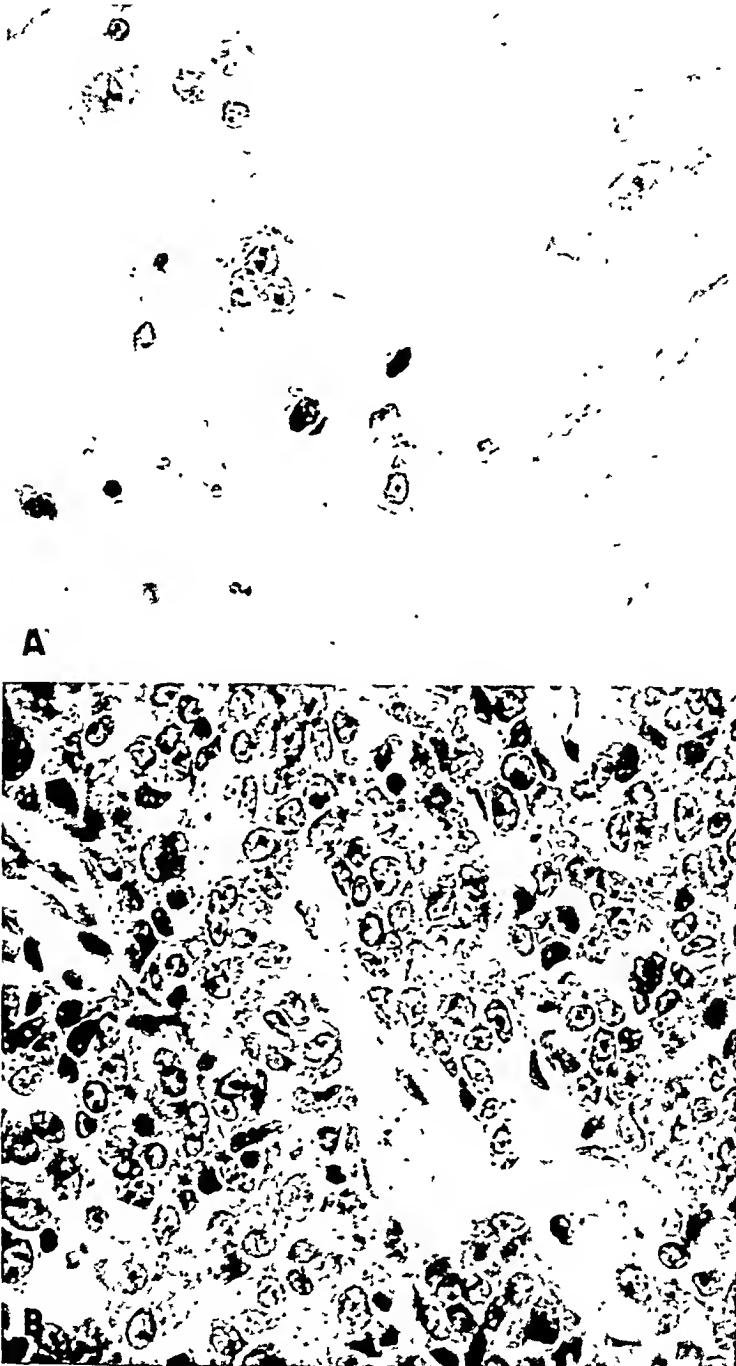


FIG. 11. A, Tumor cells demonstrating prominent nucleoli. B, Undifferentiated carcinoma from same case as A. ($\times 800$)

At first glance, the small cells shown in Fig. 11A do not appear to differ greatly from many normal cells, but on closer inspection it is clear that the nucleolus is much larger and

the prominent red nucleolus and large nucleus, the diagnosis of cancer was made and confirmed upon examination of tissue removed at autopsy. The tissue in Fig. 11B represents an undifferentiated carcinoma of the bronchus.

Figure 12A shows a smear taken from a patient with squamous-cell carcinoma of the bronchus. The cells contain black intranuclear and cytoplasmic "inclusion bodies" that are seen more clearly in the histologic section of tumor taken from the same patient (Fig. 12B).

During this study only three cases of adenocarcinoma of the lung were encountered. The smear from one case (Fig. 13A) showed a few moderately large cells with vesicular nuclei, prominent nucleoli, and a loose, vacuolated cytoplasm. On comparison with the tissue section from this tumor (Fig. 13B), the cell type in the smear was found to correspond very accurately to the cytology of the section.

The smear taken from a case of squamous-cell carcinoma of the bronchus (Fig. 14A) offers a good opportunity to compare a group of tumor cells with a group of normal cells. The cancer-cell nuclei are somewhat larger and have prominent large nucleoli. The normal cells are relatively uniform in size and

FIG. 12. A, Group of tumor cells showing dark, large, inclusion-like bodies in cytoplasm. ($\times 800$.)

more prominent than the nucleolus of a normal cell. These nucleoli were stained red, whereas the great majority of nucleoli in normal cells are blue or purple. On the basis of

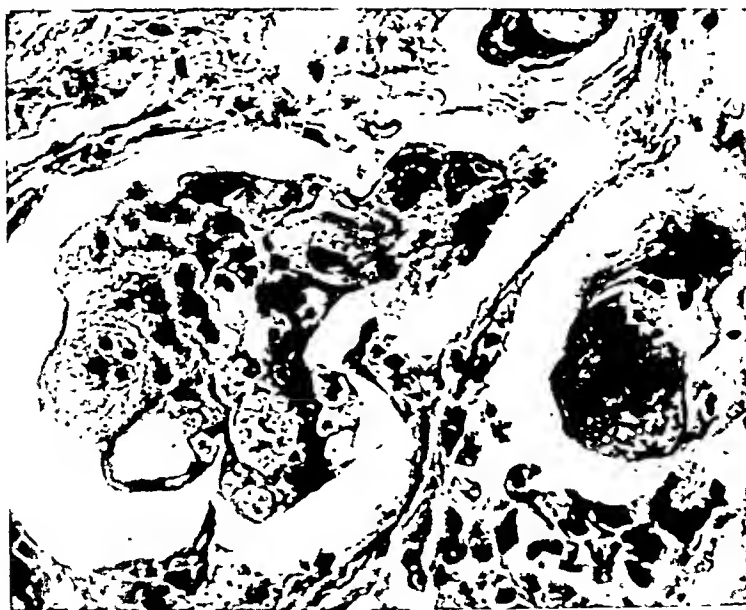


FIG. 12. B, Epidermoid carcinoma from same case as A. Note inclusion-like bodies in nuclei and cytoplasm. ($\times 800$.)



FIG. 13. A. *Tumor cells showing prominent nucleoli. ($\times 800$.)*

shape and the nucleoli are small and barely noticeable. Figure 14B shows the appearance of the tumor on histologic section.

RESULTS

Of the thirty-five cases studied at autopsy.

twenty-five were without tumor and these smears were used to gain a knowledge of the normal cytology of the smear. Six cases had bronchogenic carcinoma and four had carcinoma metastatic to the lung. All the smears from the cases of bronchogenic carcinoma

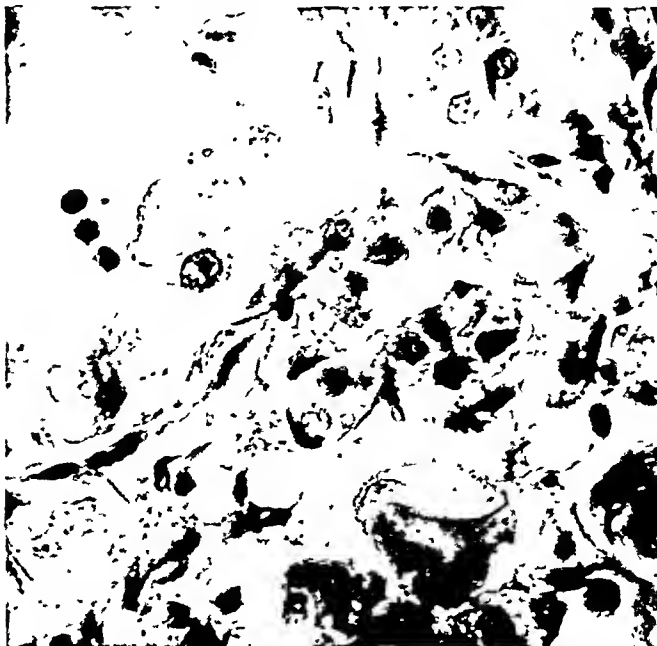


FIG. 13. B. *Adenocarcinoma from same case as A. Note prominent nucleoli. ($\times 800$.)*

showed tumor cells, but only two of those of metastatic tumor.

Table 1 gives a statistical summary of the cases examined by bronchoscopically aspirated secretions.

copy, bronchoscopic biopsy, lymph-node biopsy, cell-block examination of pleural fluid, findings at thoracotomy with or without resection, and postmortem examination. In forty-eight, there was tissue from one or more

TABLE 1
RESULTS OF ASPIRATION BIOPSY IN BRONCHOGENIC CARCINOMA

	Number	Per Cent
Total bronchoscopy cases	170	
Cases of bronchogenic carcinoma	54	
a. Histological diagnosis	48	
b. Clinical diagnosis	6	
Positive smears (54 cases of carcinoma)	40	74%
False-negative smears (Carcinoma present; smear negative)	14	26%
False-positive smears (No carcinoma; smear positive)	3	
Total errors	17	10%

	Total	Smear positive	Smear negative
Bronchoscopy positive	29 (54%)	26 (48%)	3 (6%)
Bronchoscopy negative	25 (46%)	14 (26%)	11 (20%)
TOTAL	54 cases	40 (74%)	14 (26%)

DISCUSSION

In this series of 170 cases, a diagnosis of bronchogenic carcinoma was made in fifty-four cases by an evaluation of all the available evidence. This included history, physical examination, roentgenography, bronchos-

copy, bronchoscopic biopsy, lymph-node biopsy, cell-block examination of pleural fluid, findings at thoracotomy with or without resection, and postmortem examination. In forty-eight, there was tissue from one or more

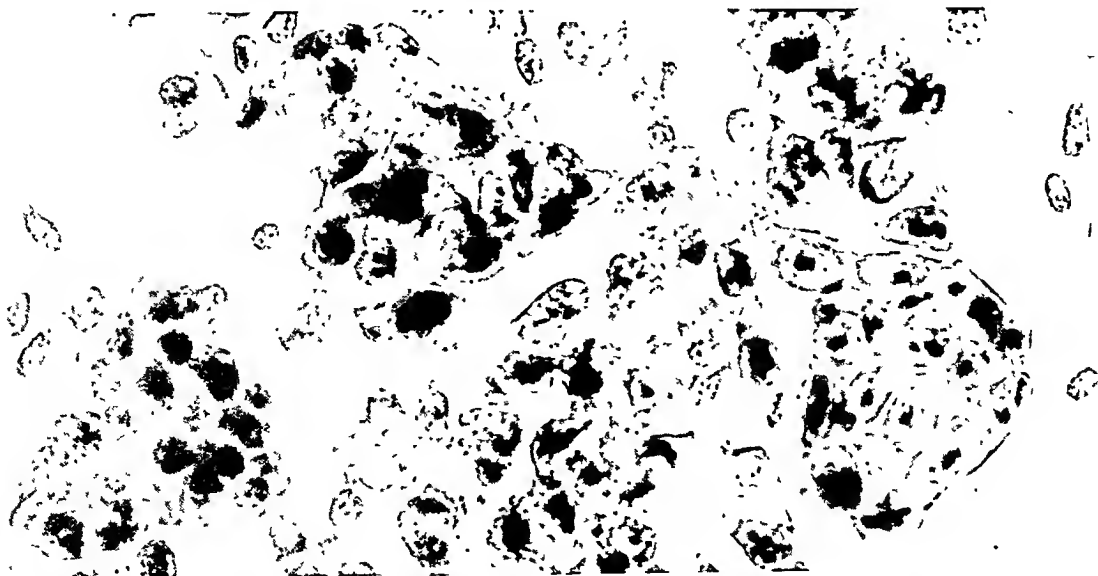


FIG. 14. A, Group of tumor cells demonstrating large nuclei and prominent nucleoli. Compare with group of normal cells to the right. ($\times 800$.)

and roentgenographic findings, phrenic or recurrent laryngeal nerve paralysis, Horner's syndrome, evidence of cerebral metastasis, bloody pleural effusion, or various combinations of these criteria of pulmonary cancer. In any event, these six cases have been included in the computation of all statistics relative to accuracy of smear diagnosis.

A positive smear by the Papanicolaou method was obtained in forty cases, or 74 per cent of the fifty-four cases; negative smears, in fourteen, or 26 per cent. "False positives" were obtained in three cases, which will subsequently be described in more detail. The total error in this group was seventeen cases, or 10 per cent, so that the technique had an over-all accuracy in our hands of 90 per cent.

In fourteen (26 per cent) of the cases of bronchogenic carcinoma, bronchoscopy was negative and the smear was positive. All of these tumors were in the left or the right upper lobe except for two in the left lower lobe. Tumors of the upper lobes are the most difficult from which to obtain biopsy specimens through the bronchoscope and in many instances no tissue can be obtained in this manner. It was the hope at the outset of this study that it would be in just such cases that

the bronchial smear would be of aid in diagnosis, and experience has borne this out: it is here that the real value of the smear method is best demonstrated.

In addition, we have recently encountered two peripheral tumors (not included in this series) that could not be visualized at bronchoscopy. In each, the smear was positive for tumor cells. In this connection it is noteworthy that the smear failed to pick up three tumors that could be seen and biopsy specimens obtained through the bronchoscope. This group, and the entire group of false-negative cases, have been reviewed and no tumor cells have been found after prolonged search. These cases are difficult to explain. Anatomically most of them were essentially similar to those that did have positive smears. It may be that not enough smears were made in each case, or that the secretions were obtained from a site not immediately adjacent to the tumor.

The three false-positive cases are of considerable interest. One patient had pulmonary tuberculosis and the diagnosis of carcinoma was based on the presence of one cell that had the appearance of a tumor cell. This demonstrates clearly that a positive diagnosis

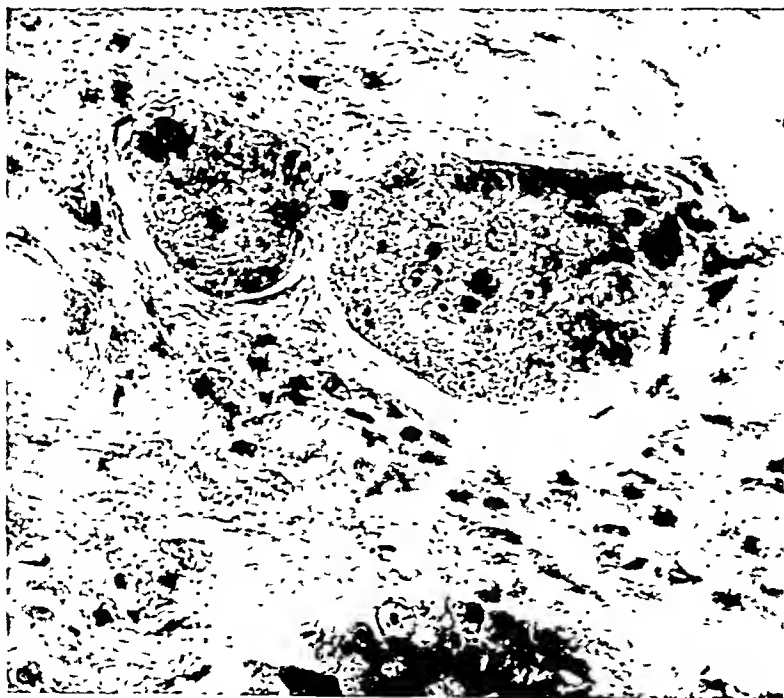


FIG. 14. B, Tissue from the same case as A. ($\times 800$.)

should not be made on the presence of only one cancer-like cell. Furthermore, it has been our experience that numerous tumor cells could be found in all instances that were unequivocally positive. The second false-positive diagnosis was made from a poorly prepared smear in which a group of columnar cells were packed together in a whorl which gave the appearance of an epidermoid pearl. These two represent errors in interpretation that are easily correctible. The third false-positive case was not of the same order, however. The patient had a bronchial polyp which occluded the lumen of the left main-stem bronchus and gave rise to atelectasis and suppurative infection of the distal pulmonary tissue. The surface epithelium of a portion of the polyp had undergone squamous metaplasia and desquamated cells were present that were and are indistinguishable from tumor cells. This case represents a limitation in cytologic diagnosis of carcinoma and is not an error of interpretation.

Because of these three false-positive cases, and particularly the last, it seems inadvisable to recommend pneumonectomy on the basis

of a positive smear alone. However, since the risk of thoracotomy is so small, it is believed that a positive smear may be an indication for thoracotomy with the findings at the time of operation determining the need for any further procedure. Several cases encountered during this study have demonstrated the advisability of thoracotomy when a positive smear is obtained.

SUMMARY

Seven hundred slides of smears of bronchial secretions obtained from 170 bronchoscopic examinations were studied. Of the fifty-four bronchogenic carcinomas encountered, tumor cells appeared on the slides of forty, or 74 per cent. Fourteen false-negative and three false-positive diagnoses were made. The smear was positive in fourteen cases (26 per cent) that were negative at bronchoscopy. It is concluded that the Papanicolaou smear of bronchoscopic aspirations is a valuable adjunct in the diagnosis of pulmonary carcinoma and that a positive smear may be an indication for thoracotomy but of itself is not an indication for pneumonectomy.

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CYTOLOGICAL STUDIES OF SPUTUM AND BRONCHIAL SECRETIONS IN THE DIAGNOSIS OF CANCER OF THE LUNG*

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RECENT studies have suggested the utility of the sputum smear in the diagnosis of bronchogenic carcinoma. Although there had been scattered earlier observations, the first extensive investigation was by Dudgeon and Wrigley in England. A great impetus to the cytological techniques in the diagnosis of cancer in general came from the work of Papanicolaou and Traut.^{5,6} The most thorough cytological and statistical study of the sputum to date has been made by Wandall. Herbut and Clerf have emphasized the value of the bronchial smear.

It has been stressed that considerable training is required before the cytological diagnosis can be practiced with accuracy. Nevertheless no completely satisfactory analysis of the accuracy of the method has as yet been made available. Such a critical analysis would require that the series under study contain a large proportion of control material drawn from patients in whom the possibility of a carcinoma is remote. We wish to emphasize this requirement, since it is obvious that any patient in whom a carcinoma is suspected on clinical grounds is very likely to harbor such a lesion—and in this case a diagnosis of carcinoma based on examination of the sputum is likely to be correct, even if the conclusion is wrongly drawn on the basis of finding metaplastic or other noncancerous epithelium. As a corollary to this first requirement, it is necessary also that the pathologist have no knowledge of the clinical status or even the age of the patient.

The extent to which these requirements have been met in previous investigations is indicated in Table 1. Only Wandall clearly separates, in a table, the results of the examination of material from patients unknown to the observer. Most previous series, including Wandall's, have included a relatively low proportion of specimens from individuals without carcinoma. The study to be reported here includes a large number of sputa from patients without carcinoma, and all of the interpretations were made by a single observer on the basis of numbered slides, with no inkling of the clinical nature of the case.

MATERIALS AND METHODS

Originally it was planned to obtain at least three sputa on separate days from each patient. This did not prove possible, since good samples could not always be produced at will, or patients were discharged or otherwise too soon lost from the study. Especially few specimens were obtained from the control patients, since their stay in the hospital was relatively brief compared to that of the patients with tumors or suspected tumors of the lung.

The sputa were collected by technicians in



FIG. 1. Squamous epithelial cells in sputum; specimen 196. ($\times 410$.)

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* Supported by a grant from the Office of Naval Research, as Project N6ori-44, Task Order XI.

The authors wish to express their appreciation to Dr. John H. Watkins of the Department of Public Health for help in considering the statistical aspects of the problem.

Received for publication, April 14, 1948.

TABLE I.

STATISTICAL ASPECTS OF CYTOLOGICAL DIAGNOSIS OF CARCINOMA

Observers	Patients known to observers	<i>Av. no. specimens from each patient</i>	No. slides from each specimen	No. pts. with ca.	No. pts. without ca.	Histol. evidence of ca.	No. correct positive diagnoses	No. false-positive diagnoses	Remarks
<i>Smears of sputum</i>									
Dudgcon & Wrigley*	?	1?	6	38	20	17/38	26/38† (68%)	1/20 5%	†At least 2 of the positive diagnoses were of metastatic carcinoma
Gowar	?	2.5	"several (c.g., 6.)"	63†	30	21/36	36/63 (64%)	0	‡Some were not primary in lung
Wandall	No§	3	1?	100	66	83/100	84/100 (84%)	6/66 (9.1%)	§Tabulated data includes only such patients. This is only part of material surveyed by Wandall
Papanicolaou ⁵	?	?	?	32	21	22-25/32	22/32 (69%)	0	
Present Report	No	2.6	1 (usually)	49	59	33/49	21/49 (42.8%)	3/58 (5.1%)	
<i>Smears of Bronchial Secretions</i>									
Herbut and Clerf	?	?	6-24	57	?	24/57	24/57 (82%)	?	
Present Report	No	1	1 (usually)	30	43	21/30	9/30 (30%)	2/43 (4.8%)	28 of these also included in the sputum group above

* Barrett reports material from the same series of cases.

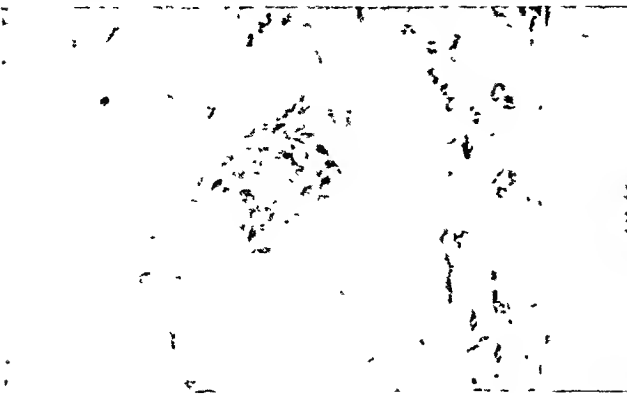


FIG. 2. *Metaplastic epithelium of squamous type; specimen 351. ($\times 240$.)*

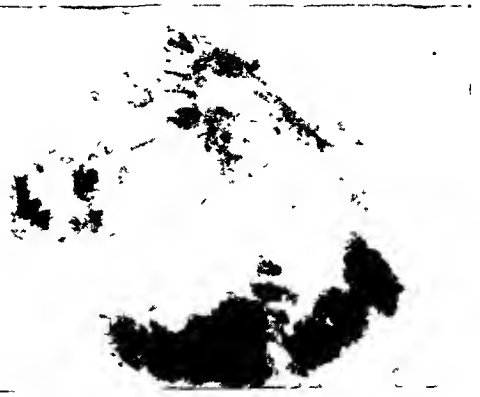


FIG. 3. *Giant cell in sputum; specimen 726. ($\times 600$.)*

clean petri dishes directly from the patient and, as soon as possible, smeared by means of platinum wires upon new slides over an area to be covered by a 22×30 mm. coverslip. The technicians were instructed in methods of teaching patients to produce samples from the lower respiratory tract and in the technique of selecting particles of true sputum, especially such as were flecked with blood or suggested tissue by their appearance. Material obtained at bronchoscopy during the earlier period of the study was collected in the form of washings, but a few smears later in the investigation were made from cotton swabs wet with the contents of the bronchi. The material was spread on the slides and fixed before drying.

The smears were fixed either in Schaudinn's fluid or in the mixture of equal parts of 95 per cent alcohol and ether recommended by Papanicolaou and Traut. Schaudinn's fluid seemed to give better results, but not to such an extent as to outweigh the convenience of the alcohol-ether method. As said, an attempt was made to obtain three sputum specimens on different days from each patient. Three slides were prepared from each specimen of which one was stained with hematoxylin and eosin, one by the Masson technique, and one with 2 per cent Gimsa solution buffered with Sørensen's phosphates at pH 6.8. Wandall's description of the staining method is excellent. Actually the vast majority of interpretations were rendered on the basis of the hematoxylin and

eosin preparations alone, and the other slides were used merely to supplement the observations; for example, in the search for fungi and to establish the staining properties of certain cells, such as the mononuclear or eosinophilic leukocytes. The slides were examined systematically with the aid of a mechanical stage so that all fields in the 22×30



FIG. 4. *Squamous-cell carcinoma. Tissue ($\times 320$) above. Clump of tumor cells ($\times 800$) below. Note sharply defined cytoplasmic boundaries of the tumor cells. (Specimens 41503 and 1212.)*

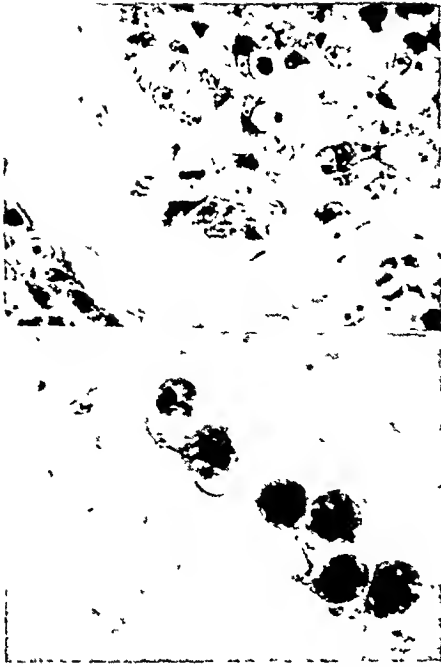


FIG. 5. *Squamous-cell carcinoma.* Tissue ($\times 320$) above. Group of tumor cells ($\times 800$) below. The cells have become separated and consequently are rounded. Two cells are in mitosis. (Specimens 39866 and 462.)

mm. area came under inspection.

There is nothing in any method of staining that will with certainty identify carcinoma cells. It is the acquired experience of the pathologist with a particular method that yields the necessary accuracy. Since the writers had had the largest experience with hematoxylin and eosin, they used this method by preference.

CRITERIA FOR DIAGNOSIS OF CARCINOMA

Reliance was placed only upon groups of cells possessing an arrangement suggesting that of tissue, not merely upon individual atypical cells. The decision was usually not difficult to make. Criteria suggesting malignancy were, in general, the same as those employed in the interpretation of histological sections, but obviously evidence of invasiveness was lacking. There was, however, variation in size, shape, and intensity of staining of the cells and of their nuclei, hyperchromatism, prominent nucleoli, and rarely, mitoses. These criteria as applied in practice

are best demonstrated in photographic comparisons of tumor and other cells (Figs. 1 to 7).

No attempt was made to differentiate the histological varieties of carcinoma, although this was possible in certain instances. It has been done, with apparent success, by Barrett and by Woolner and McDonald. The squamous-cell tumors possess irregular, large cells with well-defined outlines and often deeply eosinophilic cytoplasm (Fig. 4). In some cases there is actual evidence of keratinization or a suggestion of whorling. In some less well-differentiated epidermoid tumors the cells are smaller and the cytoplasm basophilic. Mitoses are rarely found (Fig. 5). Anaplastic carcinoma may be identified by the presence of closely crowded cells with scanty basophilic cytoplasm and very finely reticular nuclei containing many minute nucleoli. These cells seem to have a syncytial arrangement or the cells are so closely crowded in a mulberry arrangement that the nuclei appear to overlap. Most irregular and often vacuolated are the cells of adenocarci-

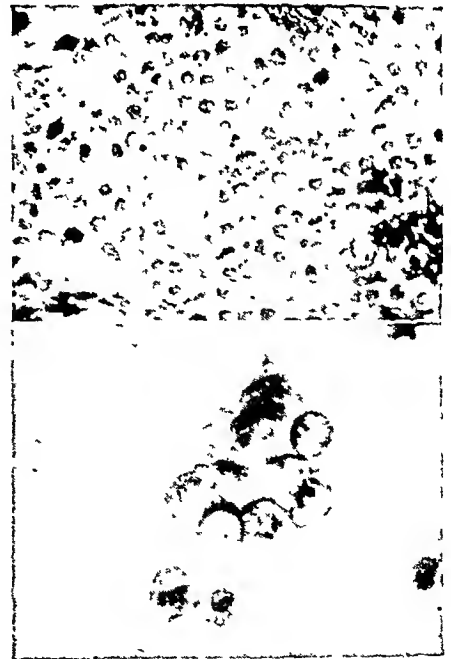


FIG. 6. *Anaplastic carcinoma.* Tissue ($\times 320$) above. Berry-like cluster of tumor cells ($\times 800$) below. Note the small amount of cytoplasm and the numerous minute nucleoli. (Specimens 42318 and 1554.)



FIG. 7. *Adenocarcinoma. Tissue ($\times 320$) above. Group of tumor cells ($\times 800$) below. Note the vacuolated cytoplasm and the vaguely defined cell boundaries. (Specimens 41181 and 1124.)*

noma. These tend least to adhere in groups (Fig. 7).

The greatest difficulty, and a source of error especially during the first six months of the study, was confusion with metaplastic epithelium, either on account of changes in the epithelium incident to its sloughing, or on account of poor histological technique. Where well preserved and stained, the cells of the metaplastic epithelium tend to vary much less in size and to possess finely reticular nuclei, with minute or no nucleoli (Fig. 2).

OBSERVATIONS

Material from 131 patients came under study. The final clinical diagnoses established in these cases are given in Table 2. More than half of the patients had no evidence of carcinoma and were deliberately chosen by the clinicians as controls. The large number of patients with bronchiectasis and tuberculosis is worthy of note. It is in such instances that possibly confusing metaplastic changes in the epithelium might be expected. Rela-

TABLE 2.
CLINICAL DIAGNOSES IN PATIENTS
SURVEYED

Bronchogenic carcinoma	51
Possibly bronchogenic carcinoma	6
Metastatic carcinoma in lung	3
Metastatic melanoma in lung	1
Adenoma of bronchus	2
Bronchiectasis	27
Tuberculosis	13
Abscess of lung	9
Pneumonitis	7
Dermoid of mediastinum	1
Asthma	1
Empyema	1
No pulmonary disease	8
Undiagnosed	1
TOTAL	131

TABLE 3.
MATERIAL SURVEYED

Material	No. patients	No. specimens
Sputum	112	294
Bronchial secretions	79	82
Sputum and bronchial secretions	60*	
TOTAL	131	376

* These are included in the other groups. Thus there are 19 patients who had an examination of bronchial secretions, but not of sputum.

tively few patients in Wandall's series had such conditions.

The types and number of examinations performed are summarized in Table 3. It is apparent that only three patients had more than one bronchoscopic examination, but that the average number of sputum examinations per patient was 2.6. Nineteen individuals (two of them with carcinoma) who had bronchoscopic examinations did not have sputum examinations. It is desirable to analyze the data concerning the sputa and the bronchial secretions separately, and then to compare them. In each group the number of examinations per patient is indicated, since the ideal of having the same number in each group was not achieved for reasons mentioned before.

The data concerning the sputum specimens are collected in Tables 4 and 5. Table 4 presents the fundamental data; Table 5 shows

in detail the number of examinations of sputum made in the various diagnostic groups. In the group tabulated as "Carcinoma" there was usually histological confirmation, or overwhelming roentgenographic and other clinical evidence of the disease. In the "Possibly carcinoma" group the roentgenographic diagnosis was less certain although the diagnosis of carcinoma stood first among the probable diagnoses. In those cases listed under "No carcinoma" some other diagnosis was generally established, although it is possible that subsequent investigation may reveal the existence of carcinoma. Twenty-nine positive diagnoses for twenty-five patients were returned from the sputum studies. In twenty-one patients in whom the sputum examination was correctly reported as positive, the clinical diagnosis of carcinoma was established as follows:

Confirmed by bronchial biopsy	4
Confirmed by biopsy of peripheral node	3
Confirmed by tissue removed at thoracotomy	11
No tissue confirmation, but supported by strong roentgenographic and other clinical evidence	3
	21

Thus there was histological confirmation of the diagnosis in approximately 85 per cent of the patients. In the remaining three in the "Carcinoma" group of Table 4, roentgenographic and other clinical evidence made the diagnosis virtually certain.

Of special interest are the three in the "No carcinoma" group in whom a positive diagnosis was returned in the sputum examination. One of these was a man of 22 years with

TABLE 4.
DIAGNOSES BASED ON SPUTUM SMEARS
IN RELATION TO FINAL DIAGNOSES

Final diagnosis	Sputum smears		
	No positives	At least one positive	Total patients
Carcinoma	28	21	49
Possibly carcinoma	3	1	4
No carcinoma	56	3	59
TOTAL PATIENTS	87	25	112

bronchiectasis of the right middle and lower lobes. These were removed operatively, with confirmation of the diagnosis and no evidence of cancer (Fig. 8). The second patient (Fig. 9, Spec. 232) was a man of 42 years who had had repeated hemoptyses. He was observed at the New Haven Hospital in November, 1946. Bronchoscopy did not reveal a carcinoma and bronchograms showed evidence of minimal cylindrical bronchiectasis in the anterior pectoral segment of the right upper lobe. His last recorded chest examination was at the end of March, 1947. At that time he had no further complaints, although occasional moist râles were audible in the region of the right middle lobe. The third patient (Fig. 10), a man of 44 years, was admitted in October, 1946, complaining of shortness of breath, "soreness" in the chest, and a weight loss of 16 pounds. He had had "pneumonia" in February, 1946, from which he recovered following penicillin treatment. Bronchograms

TABLE 5.
NUMBER OF SPUTUM SMEARS IN RELATION TO NUMBER OF PATIENTS AND
DIAGNOSTIC CATEGORIES

A. Number of sputum smears per patient	B. Total patients in relation to final diagnoses				C. Total number of sputum smear diagnoses			D. Number of sputum smear diagnoses in relation to final diagnoses					
	All	Ca.	Possibly ca.		All	Pos.	Neg.	Ca.		Possibly ca.		No ca.	
			ca.	No ca.				Smear positive	Smear negative	Smear positive	Smear negative	Smear positive	Smear negative
1	29	5	1	23	29	2	27	2	3	0	1	0	23
2	23	10	0	13	46	4	42	4	16	0	0	0	26
3	39	21	3	15	117	18	99	14	49	1	8	3	42
4	13	5	0	8	52	2	50	2	18	0	0	0	32
5	3	3	0	0	15	0	15	0	15	0	0	0	0
6	1	1	0	0	6	0	6	0	6	0	0	0	0
7	3	3	0	0	21	2	19	2	19	0	0	0	0
8	1	1	0	0	8	1	7	1	7	0	0	0	0
TOTAL	112	49	4	59	294	29	265	25	133	1	9	3	123

showed evidence of slight cylindrical bronchiectasis in the middle and posterior basal segments of the lower lobes bilaterally, and bronchoscopy revealed "inflammatory changes" in the mucosa of the left lower-lobe bronchus. These last two patients will be followed with special interest.

In order to arrive at an estimate of the ac-

curacy of the method, the cases considered as "Possibly carcinoma" are ignored. An alternative scheme, not employed in the present analysis, is to arrive at a range of percentages by considering the doubtful cases variously as all cases of carcinoma, or as all noncarcinomatous. The following estimates are based on Tables 4 and 5.

1. Percentage of Correct Positive Diagnoses

$$\begin{aligned} \text{a. Based on patients} &= \frac{\text{No. of patients diagnosed as positive correctly}}{\text{No. of patients with carcinoma}} \\ &= 21/49 \text{ (42.8 per cent).} \end{aligned}$$

(Average number of sputa per patient in this group = 3.2).

$$\begin{aligned} \text{b. Based on sputum examinations} &= \frac{\text{No. of sputa reported positive correctly}}{\text{No. of sputa from patients with carcinoma}} \\ &= 25/158 \text{ (15.8 per cent).} \end{aligned}$$

The complements of the calculated percentages yield the percentages of incorrect negative diagnoses based on patients and sputum examinations, respectively 57.2 and 84.2 per cent. Thus it appears that if three sputa rather than one are examined, the incidence of correct diagnoses is increased some 2½ times. Examination of Table 5, however, reveals an apparent inconsistency, since when four or more sputa were examined, the incidence of positive smears appeared to decrease (compare column B [Final diagnosis carcinoma], with column D [Positive smear diagnoses in patients with carcinoma]). Upon further analysis, it is evident that more than three sputa were examined in those patients in whom the diagnosis was strongly suspected on clinical grounds but in whom no positive sputa were obtained in the first three examinations.

2. Percentage of False Positive Diagnoses

$$\begin{aligned} \text{a. Based on patients} &= \frac{\text{No. of patients diagnosed positive incorrectly}}{\text{No. of patients without carcinoma}} \\ &= 3/59 \text{ (5.1 per cent).} \end{aligned}$$

(The average number of sputa examined per patient in this group = 2.1.)

The complements of these calculated percentages yield the percentages of correct negative diagnoses based on patients and sputa respectively: 94.9 and 97.6 per cent.

3. Incidence of False Positive Diagnoses among all Positive Smears Diagnosed

This value is obtained from column D in Table 5, ignoring patients with the unconfirmed possible final clinical diagnosis of carcinoma, = 3/28 = 10.7 per cent.

BRONCHIAL SECRETIONS

Tables 6 and 7 summarize the observations made on the bronchial secretions. Of nine patients in whom a correct diagnosis was returned, there was histological confirmation in seven:

Confirmed by bronchial biopsy	4
Confirmed by biopsy of peripheral nodes	1
Confirmed by tissue removed at thoracotomy	2
No tissue confirmation, but supported by strong roentgenographic and other clinical evidence	2
	9

Corresponding values can be calculated from the data in Tables 6 and 7, for the patients in whom bronchial secretions were examined, as follows:

1. *Percentage of Correct Positive Diagnoses* = 30 per cent (9/30).
(Incorrect negative diagnoses in patients with carcinoma = 70 per cent [21/30]).
2. *Percentage of false positive diagnosis* = 4.7 per cent (2/43).
(Correct negative diagnoses = 95.3 per cent [41/43]).
3. *Incidence of false positive diagnoses among all smears diagnosed as positive* = 16.7 per cent (2/12).

TABLE 6.
DIAGNOSES BASED ON BRONCHIAL
SMEARS IN RELATION TO
FINAL DIAGNOSES

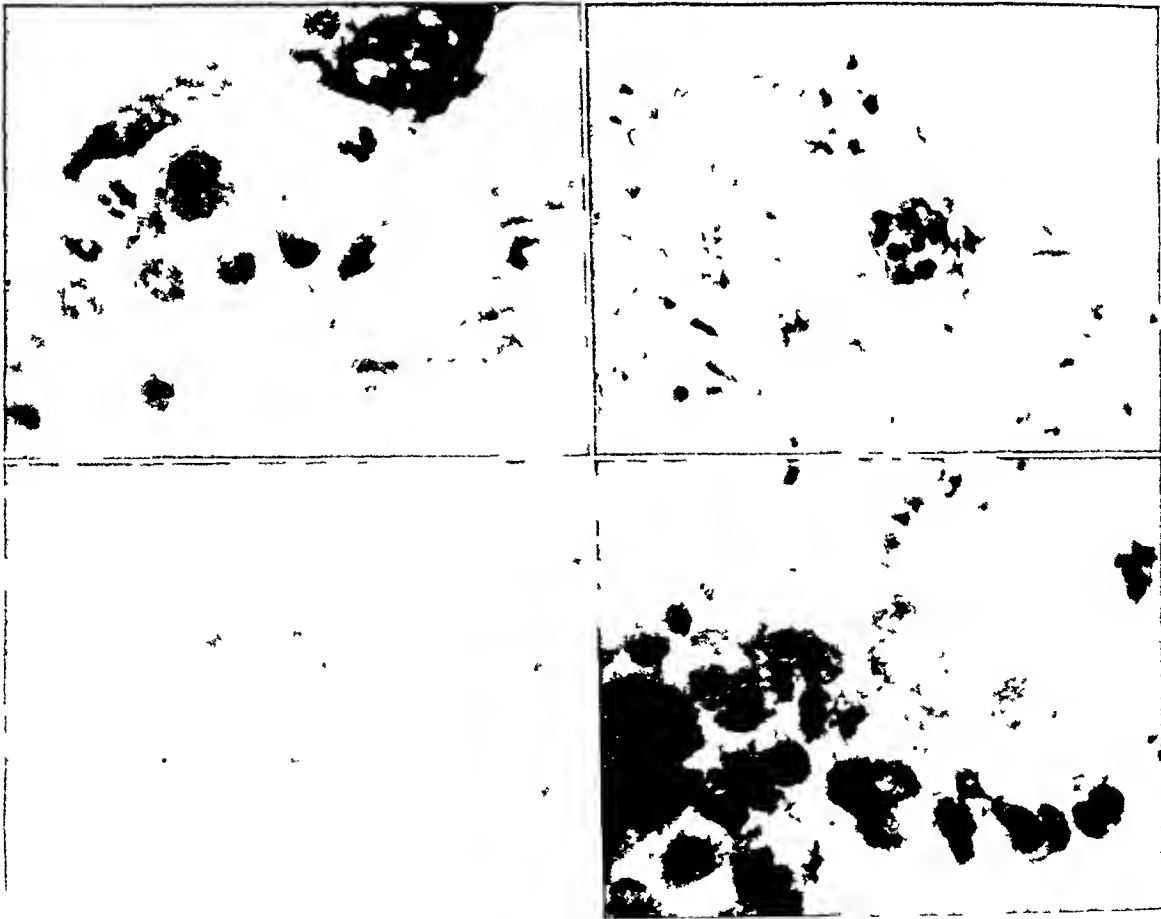
Final diagnosis	Bronchial smears		Total patients
	No positives	At least one positive	
Carcinoma	21	9	30
Possibly carcinoma	5	1	6
No carcinoma	41	2	43
TOTAL PATIENTS	67	12	79

In the "false positive" group of the bronchoscopic series, one patient, aged 27, showed bronchographic evidence of bronchiectasis. The other, (Fig. 11) a man of 45 years, was proved at operation to have a small abscess of the middle basal segment of the lower lobe

with a large zone of organizing pneumonitis. He died following a resection, but autopsy permission was unfortunately not obtained.

COMPARISON OF EFFECTIVENESS OF THE SPUTUM AND BRONCHIAL SMEAR TECHNIQUE

In comparing the diagnoses based on material from the two sources, it must be remembered that only three of the seventy-nine patients in whom a bronchoscopy was performed had more than one examination; on the contrary, the average number of sputum examinations was 2.6. Consequently, the basis for comparison should be the results of examination of a single bronchial secretion and those of a single sputum. On this basis, as can be seen from Table 8, which summarizes the data of the preceding section, the bronchial-smear method appears to be roughly twice as sensitive as the sputum-



FIGS. 8-11. Groups of tumor cells incorrectly considered to represent carcinomatous tissue. FIG. 8. Upper left: Specimen 705 ($\times 743$). FIG. 9. Upper right: Specimen 232 ($\times 297$). FIG. 10. Lower left: Specimen 196 ($\times 297$). FIG. 11. Lower right: Specimen 1223 ($\times 743$). See text for clinical data.

TABLE 7.

NUMBER OF BRONCHIAL SMEARS IN RELATION TO NUMBER OF PATIENTS AND DIAGNOSTIC CATEGORIES

Number of bronchial smears per patient	Total patients in relation to final diagnoses				Total number of bronchial smear diagnoses			Number of bronchial smear diagnoses in relation to final diagnoses					
	All	Ca.	Possibly ca.	No ca.	All	Positive	Neg	Ca.		Possibly ca.		No ca.	
								Smear posi- tive	Smear nega- tive	Smear posi- tive	Smear nega- tive	Smear posi- tive	Smear nega- tive
1	76	29	5	42	76	10	66	8	21	0	5	2	40
2	3	1	1	1	6	3	3	2	0	1	1	0	2
TOTAL	79	30	6	43	82	13	69	10	21	1	6	2	42

smear method in arriving at a correct positive diagnosis, but the incidence of false positives also appears to be twice as great. The number of examinations, particularly of the

TABLE 8.

COMPARISON OF DIAGNOSES:
SPUTA VS. BRONCHIAL SECRETIONS

Material	% Correct positives	% False positives	Average no. of specimens
Sputum	42.8	5.1	2.6
Sputum	15.8	2.4	1.0
Bronchial secretions	30.0	4.7	1.1

bronchial secretions, is so few, however, that a single diagnosis made in a direction opposite to what was actually the case would have a considerable effect on the percentages. Consequently, more data must accumulate before a final evaluation becomes possible.

RELATION OF LOCATION OF TUMOR TO
RESULTS OF CYTOLOGICAL STUDY

Of paramount importance in evaluating the cytological technique would be the determination of how early tumors of the lung can be diagnosed by this means. This can only be established through the use of the technique as a method of "screening" large numbers of individuals as has been accomplished, with considerable success, in the case of vaginal smears. Sputum, however, can be obtained only in such individuals as produce it. The method must therefore be practiced on large numbers of patients, especially in the older age groups, who produce sputum, whether or not the clinical diagnosis suggests carcinoma, and routinely on secretions obtained at bronchoscopy. This is an arduous undertaking which has not as yet been prac-

ticed on a sufficiently large scale to yield a significant amount of follow-up data.

Another approach to the evaluation is to correlate the results of the cytological examination with the position of the tumor as determined by examination of the operative specimens. This was possible in the seventeen pneumonectomies that were performed in the present group of fifty-one patients with carcinoma. Tumors involving the orifices of the segmental bronchi (in the sense of Brock or Boyden) or any of the more proximal bronchi, are considered "central." Tumors involving the branches of the segmental bronchi are considered peripheral. An example of the type of tumor from which a positive sputum was obtained is shown in Fig. 12. The results as indicated in Table 9

TABLE 9.

RELATION OF LOCATION* OF TUMOR
TO RESULT OF CYTOLOGICAL STUDY

Result of cytological study	Tumor central	Tumor peripheral
Positive	7	2
Negative	3	5
TOTAL	10	7

* Based on examination of lung removed at operation.

are discouraging, in that most tumors yielding identifiable carcinoma cells in the smears were centrally located. Peripheral tumors usually yielded negative results. Moreover, all of the resected tumors were of large size. A similar correlation attempted on the basis of roentgenographic studies gave less clear-cut results, probably for the reason that the location of the tumor is more difficult to establish by this method. The peripheral tumors present a smaller surface to the bron-



FIG. 12. Specimen removed at operation. Epidermoid carcinoma projecting into middle basal bronchus of right lower lobe. Most tumors yielding detectable tumor cells in the sputum were of this central type. The tumor cells found in the sputum of this case and a histological section are illustrated in Fig. 5. The tumor has invaded a major branch of the pulmonary artery and extended within and along the vessel into the anterior basal segment which has been separated by a partial incision from the middle basal segment.

chus and are furthermore connected with the exterior by a longer, more tortuous, and less easily draining channel within which the tumor cells may more readily undergo autolysis.

It remains to inquire what contribution is made by the cytological technique in establishing the microscopic diagnosis of cancer preoperatively over and above what is contributed by bronchoscopy. For this purpose there were selected from the total of fifty-one patients with carcinoma, the forty-two in whom bronchoscopy was performed with biopsy of suspicious lesions, and who also had at least one sputum examination. It is apparent that the sputum examinations doubled the number of cases with microscopic evidence of cancer, i.e., cells suggest-

ing the existence of carcinoma were found in 38 per cent (16 of 42) by examination of the sputum, in addition to the 38 per cent (16 of 42) in whom a positive diagnosis was established by bronchoscopic biopsy. These results are correlated in Table 10.

TABLE 10.
DIAGNOSTIC RESULTS IN PATIENTS
WITH BOTH BRONCHOSCOPIC AND
SPUTUM EXAMINATIONS

Result of bronchoscopic examination	Result of Sputum Examination	
	Positive	Negative
Positive (16 patients)	4	12
Negative (26 Patients)	16	10
TOTAL 42	20	22

From Table 11 it is apparent that the bronchial smears contributed an additional 17 per cent (5 of 30) of positive microscopic diagnoses to the 37 per cent (11 of 30) avail-

acy of the method in practice by groups of technicians, rather than of fully-trained pathologists, is necessary. Such an investigation should also indicate the time necessary to train technical personnel, and the sources of personal variations in arriving at diagnostic conclusions.

TABLE 11.
DIAGNOSTIC RESULTS IN PATIENTS
WITH BRONCHOSCOPIC EXAMINATIONS.
AND BRONCHIAL SMEARS

Result of bronchoscopic examination	Result of Bronchial Smear	
	Positive	Negative
Positive (11 Patients)	4	7
Negative (19 Patients)	5	14
TOTAL 30	9	21

able from the bronchoscopic biopsies. In the group with negative bronchoscopic biopsies, there was only one patient with a positive bronchial smear who had a negative sputum.

DISCUSSION

A more detailed study embracing a larger body of cytological and clinical material could be carried out with advantage. It is important to determine the quantitative variation from slide to slide, and thus the optimum practical number of specimens and slides to be examined.

It is obvious that most of the work of screening will have to be carried out by technicians. Consequently, a study of the accu-

SUMMARY AND CONCLUSIONS

When an average of 3.2 sputum examinations was carried out in a series of patients with carcinoma of the lung, a correct diagnosis was reached from the cytological examination in 42.8 per cent. False-positive diagnoses were reported in 5.1 per cent of a group of patients without carcinoma, in whom the average number of examinations was 2.1. Bronchoscopic smears (usually one for each patient), yielded 30 per cent of correct positive diagnoses, and 4.7 per cent of false-positive diagnoses. Most tumors yielding positive smears were centrally located, and all of the resected tumors were of large size. The cytological technique increased the percentage of preoperative microscopic diagnoses to 76 per cent from the 38 per cent available from bronchoscopic biopsies alone.

These results suggest that the cytological method is a useful tool in the diagnosis of bronchogenic carcinoma. A negative result does not, however, indicate the absence of carcinoma.

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BRONCHOGENIC CARCINOMA

A Comparison of Two Consecutive Series of One Hundred Cases Each

GUSTAF E. LINDSKOG, M.D., and WILLIAM E. BLOOMER, M.D.*

IN an effort to present a comprehensive picture of therapy in bronchogenic carcinoma, a study was published in 1946² concerning a consecutive series of 100 primary pulmonary cancers seen on the thoracic surgical service of the New Haven Hospital during a five-year period ending December, 1943. In the succeeding three-and-a-half years, a second group of 100 has accumulated, the results of which are set forth to determine whether or not changes in the diagnostic and therapeutic picture may be demonstrated. The statistics for the two series will be presented in parallel fashion for comparison, and in combined form as a summary for the whole experience since 1938.

VITAL STATISTICS

The second series (or century) included ninety-six men and four women, a ratio of 24 to 1. Ninety-nine were white and one colored, a ratio again very close to that of the racial distribution in Connecticut as reported in the 1940 census. The average age of patients was 57.4 years, as compared with 54.8 in the first century. The youngest was 37 and the oldest 78 years of age. The majority of cases again fell in the sixth and seventh decades.

SYMPTOMATOLOGY

The first reported symptom to appear was cough in fifty-nine cases, chest pain in ten, hemoptysis in eight, dyspnea in seven, weakness in four, "pneumonia" in three, wheez-

ing in two, and hoarseness in two. Persistent low-grade fever, shoulder pain, appearance of an abdominal mass, and headache were each the first complaints in four other patients, while a fifth was completely asymptomatic when the diagnosis was made. Thus cough and chest pain were the two most common first symptoms in both series, while hemoptysis was again the cause of first complaint in less than 10 per cent.

TABLE I
AVERAGE DURATION OF SYMPTOMS
PRIOR TO FIRST ADMISSION
(in Months)

	1st series	2d series	Both series
Entire Group	6.7	9.1	7.9
Inoperable	6.7	8.5	7.6
Explored	6.8	7.4	7.1
Resected	7.2	9.4	8.3

The average duration of symptoms prior to the first hospital admission (Table I) tended to be significantly longer in the second hundred cases, namely 9.1 months, as opposed to 6.7 for the first series. As before, paradoxically, the inoperable group was found to have had symptoms over a somewhat shorter period of time than had the group with resectable lesions.

LOCATION OF THE PRIMARY LESION

In the second century of cases the right lung was affected in forty-eight and the left in fifty. There was bilateral lymphatic involvement in two. The upper lobes again were the site of origin in more than half (57 per cent) of the cases, a fact which helps explain the difficulty in obtaining positive bronchoscopic biopsies in a significant percentage of these cases.

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Acknowledgment is made of assistance with follow-up of case material by the Tumor Registry, which has received support in part from the Jane Coffin Childs Fund.

Received for publication, March 18, 1948.

TABLE 2
TISSUE DIAGNOSIS—BRONCHOGENIC CARCINOMA

	1st series	2d series	Both series
Positive			
<i>Living</i>	77	80	157
<i>Autopsy</i>	5	5	10
Total	82	85	167 = 83.5%
Negative	18	15	33
Method by which positive diagnosis was first established in living:			
Bronchoscopy	28	30	58 = 29%*
Thoracotomy and biopsy	10	22	32 = 16%
Lymph-node biopsy	10	12	22 = 11%
Resection, lung	10	9	19 = 9.5%
Sedimentation, pleural fluid	5	5	10 = 5%
Needle biopsy, lung	5	2	7 = 3.5%
Biopsy, metastasis	7	0	7 = 3.5%
Thoracoscopy	2	0	2 = 1.0%
TOTAL	77	80	157 = 78.5%

* 38.6% of cases bronchoscoped.

TISSUE DIAGNOSIS

A positive tissue diagnosis (Table 2) was obtained in eighty-five of the second series as compared to eighty-two of the first. This includes five cases in which tissue diagnosis was not obtained until postmortem examination. In the eighty cases of the second series in which tissue diagnosis was made during life, it was most frequently made first by bronchoscopic biopsy (thirty cases, or 38 per cent, of the bronchoscopic attempts), next by exploratory thoracotomy (twenty-two cases). In other words, of the forty explorations, 77 per cent were performed diagnostically. During the past year a study of the cytology of sputa, and of bronchial secretions obtained at endoscopy, has been carried out in most cases, and a critical evaluation of this diagnostic technique is being published.¹ However, a large number of the patients in this series were seen before this cytological study was begun, so that figures cannot be presented based on the whole group. It can be said, however, that, in the hands of a pathologist well trained in the normal variations of cellular material to be found in sputa and bronchial secretions, this technique can be of considerable value. The use of needle biopsy has

been reserved for those inoperable cases in which other techniques have failed and a positive tissue diagnosis was required before starting roentgen-ray therapy.

The tumors of the second series were classified histologically as epidermoid, forty-nine; adenocarcinoma, seven; and anaplastic, twenty-three. Six were not classifiable, because of poorly differentiated metastatic tumor or pleural-fluid cells. No tissue diagnosis was obtained in fifteen although the clinical course was typical and fatal. In the first series, adenocarcinoma seemed more frequent in the youngest decades, but in the second century there was only one patient between the ages of 30 and 39 years and his carcinoma was of the epidermoid type.

THERAPY STATUS

Fifty-seven of the second group were found to have stigmata of inoperability when first seen, and three more refused treatment (Table 3). Of the fifty-seven, twenty-eight were proved to have metastases by biopsy or by involvement of mediastinal nerves. There was evidence for presumed metastasis in fourteen. Eight patients were inoperable because the tumor encroached on the trachea as re-

TABLE 3
THERAPY STATUS

	1st series	2d series	Both series
Presumed operable and explored			
<i>Not resectable</i>	20	19	39
<i>Resected</i>	12	21	33
Total	32	40	72 = 36%
Inoperable	65	57	122 = 61%
Refused treatment	3	3	6 = 3%
TOTAL	100	100	200

vealed by bronchoscopy; six, because they were in a terminal state when first seen; and one, because the ventilatory function was so markedly restricted as to preclude any procedure that would further reduce the ventilatory capacity.

In the remaining forty patients, exploration was performed and twenty-one resections, all pneumonectomies, were carried out (52.5 per cent). In ten of these it was evident at the time of operation that the growth had extended beyond the point where cure was within the realm of reasonable possibil-

ity. Of these, eight had parietal or mediastinal infiltration by tumor. In one, a large tumor thrombus was found in the pulmonary artery; it was possible to dislocate the thrombus from the proximal pulmonary artery stump before ligating that vessel. Finally one had marked involvement of the hilar nodes, but a pneumonectomy was performed with excision of the grossly involved nodes.

The average age of those resected in the second series was 57.7 years, a figure not significantly different from the average age of the entire series (57.5). The oldest patient upon whom resection was done was 72 years of age.

RESULTS OF TREATMENT

In the second century of cases, twenty-six received no definitive therapy, and twenty-five of these are dead (Table 4). In this untreated group the range of survival after first admission to the hospital was from 0.2 to 19.3 months, averaging 3.6 months. The one patient in this group who survives has lived only 3.3 months since admission. Roentgenotherapy without major surgical intervention was used in thirty-four, of whom thirty-one

TABLE 4
PRESENT STATUS*

	Duration of life after first admission in months								
	1st Hundred			2d Hundred			Combined Series		
	Cases	Mean (mos.)	Ex- tremes (mos.)	Cases	Mean (mos.)	Ex- tremes (mos.)	Cases	Mean (mos.)	Ex- tremes (mos.)
Dead: 184 (92%)									
No special treatment	38	5.0	1-36	25	3.6	0-19	63	4.4	0-36
X-ray or radon therapy	29	7.4	2-33	31	4.7	0-15	60	6.0	0-33
Exploratory thoracotomy	9	8.0	2-26	8	2.6	0-5	17	5.5	0-26
Exploration and x-rays	12	14.9	6-50	9	13.2	3-25	21	14.2	3-50
Pneumonectomy									
Hospital deaths	3	1.6	1-2	3	1.3	0-2	6	1.5	0-2
Later deaths	5	7.4	3-26	10	5.2	2-11	15	5.9	2-26
Lobectomy	2	31.0	26-36	0			2	31.0	26-36
Living: 16 (8%)									
	1st Hundred			2d Hundred					
	Cases	Time since admission (mos.)		Cases	Time since admission (mos.)				
Pneumonectomy	2	(86, 65)		8	(32, 18, 16, 14, 10, 10, 8, 2)				
X-ray therapy	0			3	(11, 7, 5)				
Exploration and x-rays	0			2	(6, 6)				
No treatment	0			1	(3)				

* As of July 1, 1947.

are dead; the survivals ranged from 0.3 to 15.2 months, with an average of 4.7 months. In the nineteen cases found not resectable at exploratory thoracotomy, there were no operative or hospital deaths. Eleven of these had subsequent roentgen therapy and of these eleven, nine are dead, with a survival range of 3.2 to 25.3 months, averaging 13.2 months. The two still alive have survived 5.6 and 6.1 months. The eight who were explored but had no subsequent roentgen-ray therapy had a survival range of 0.3 to 5 months, with an average of 2.6 months.

Three patients of the second series died in the hospital following total pneumonectomy (14.3 per cent of twenty-one pneumonectomies). One, aged 64 years, had had episodes of paroxysmal auricular fibrillation during the operative procedure; although in apparently good condition at the close of the operation, he later had a sudden cardiac arrest. The second, a man of 66 years, had electrocardiographic evidence of left bundle branch block preoperatively. He developed left heart failure and died on the fourteenth postoperative day. The third, a man of 45 years, succumbed on the fifth postoperative day with marked pulmonary edema to clinical examination; no postmortem examination was obtained.

Ten of the eighteen who survived resection have died of metastases after periods of from 2.2 to 10.5 months, with an average of 5.2 months.

Fourteen patients of the second series are still living. This group includes eight who had pneumonectomy, with survival periods of 32, 18, 16, 14, 10, 10, 8, and 2 months (as of July 1, 1947). Three patients given roentgenotherapy alone have survived 11, 7, and 4 months. Two patients treated with roentgen rays following exploratory thoracotomy have lived 5 and 6 months. One receiving only symptomatic treatment has lived 3 months.

Five of those surviving pneumonectomy are asymptomatic and without clinical recurrence or metastasis at 32, 18, 14, 10, and 8 months respectively. The other three have evidence of metastatic foci and are losing ground rapidly after survival periods of 16, 10, and 2 months.

DISCUSSION

A comparison of the two consecutive series of cases, each of one hundred, gives little reason for optimism. The exploratory-thoracotomy rate has increased only slightly (from 32 to 40 per cent), which does not suggest that patients with lung cancer are visiting their physicians much earlier than before or that the diagnosis is being made earlier in our Connecticut communities. The percentage of resections has risen from 12 per cent of the total (38 per cent of all explorations) to 21 per cent (or 52 per cent of all explorations). Superficially, this might seem to represent progress. More accurately it reflects an increased willingness to carry out so-called "palliative" resections in hopeless cases.

Of the original century, three who had had resections were living at the time of publication. One of these, lobectomized, has succumbed to metastases and the other two are quite well at seven and five years. In the present series of one hundred, it will be seen that only five are potential candidates for five-year survival.

SUMMARY

Taking both series together it appears to be our experience that in an unscreened (*not preselected*) series of cases of bronchogenic carcinoma seen in a general hospital more than half (61 per cent) are unsuitable for exploration when first hospitalized; that not more than half of the explored cases (46 per cent) will be resected, that one in five of the resections (19 per cent) will be a hospital mortality, and that less than 5 per cent of the original group will survive five years.

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OBSCURE AXILLARY LYMPH-NODE METASTASIS IN CARCINOMA OF THE BREAST*

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THE prognosis for the patient with carcinoma of the breast depends most commonly upon the presence or absence of metastases in the axillary lymph nodes. Statistical studies have disclosed that five-year cures are encountered more often in those instances in which the surgical pathologist has been unable to demonstrate such metastases. It is evident, of course, that the accuracy of the prognosis lies in the care and thoroughness with which the regional nodes are removed by the surgeon and examined by the pathologist. In this respect, the statistical findings of Greenough, and MacDonald, are noteworthy. Both used the classification of the American College of Surgeons which is based upon the presence or absence of lymph-node metastasis as demonstrated by the pathologist. In spite of the fact that the lymph nodes were reported uninvolved, a number of fatalities from the spread of carcinoma occurred within the five-year period. Wintz reported a survey of 25,000 cases of carcinoma of the breast. These were classified according to Steintal into groups I, II, and III, where group I is that in which the primary tumor is freely movable and regional nodes are uninvolved. Here again only 75 per cent of the group, theoretically with the most favorable prognosis, showed five-year cures. Such discrepancies can, perhaps, be explained by the fact that either carcinomatous lymph nodes were left behind in the axilla, or that not sufficient histologic sections were cut from the nodes. Hence, further sectioning might have disclosed carcinoma cells in lymph nodes reported as uninvolved.

It is obvious that the presence of early

axillary metastases in carcinoma of the breast cannot be ascertained by physical examination; gross pathological examination may suffice, but ordinarily careful histologic study is required—sometimes even of serial sections of seemingly uninvolved nodes.

Little information about the presence of tumor is obtained by noting the size or firmness of the lymph nodes. Greenough in his review of 774 breast carcinomas found that, of 215 in which regional nodes were enlarged, 195, or 90 per cent, contained tumor. Yet of 135 in which they were not clinically enlarged, 55, or 40 per cent, revealed metastases when examined histologically. Mills found carcinomatous metastases that were too small to be detected clinically in approximately 50 per cent of the regional lymph nodes.

It is apparent from the surgical material of the Michael Reese Hospital that routine sections of the axillary lymph nodes failed to disclose metastases in certain instances although a carcinoma of the breast was highly malignant histologically. In each instance all palpable lymph nodes in the axilla had been dissected out and examined histologically, but only one or two microscopic sections had been cut from each node. Ten pathologists heading large surgical laboratories were questioned for information on the number of sections of axillary lymph nodes taken routinely in carcinomas of the breast. The replies placed more emphasis on the number of nodes examined than on the number of sections taken from each. Most, however, affirmed that only one section was taken from each block. Only one pathologist stated that, in the attempt to uncover early metastases, numerous frozen and fixed sections were taken from nodes that had been found negative. The question thus arose, whether or not a very few sections taken from the lymph nodes are sufficient to indicate the presence

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* This work was supported by Grant No. 708 from the American Medical Association.

Received for publication, November 20, 1947.

or absence of metastases, or whether such routine examinations are totally inadequate and should be replaced by serial sections of each lymph node that at first was found uninvolved. The following is a report of a study

mor embolus could be seen to break up into multiple small isolated clumps of cancer cells. In other instances the embolus remained intact and tumor cells invaded massively parts of the adjacent lymphadenoid tissue.

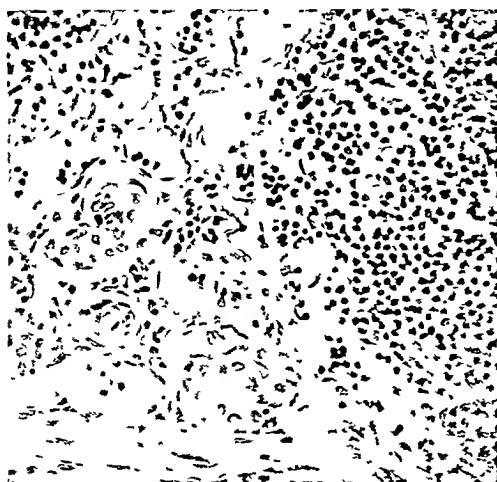


FIG. 1. Carcinoma cells in the marginal sinus, just beneath the capsule of the lymph node. (Iron-hematoxylin-eosin preparation. $\times 112$.)



FIG. 2. Carcinoma cells in lymph nodes, massively infiltrating. (Iron-hematoxylin-eosin preparation. $\times 112$.)

of serial sections of axillary lymph nodes taken from patients with carcinoma of the breast, where a few random sections had shown no tumor in the nodes.

Thirty cases of carcinoma of the breast have been studied. Serial sections were made of all axillary lymph nodes that were found in the radically operated specimens and alternate slides were stained with hematoxylin and eosin and examined. An average of 332 sections were cut from each block. A total of 149 axillary lymph nodes were examined.

The serial sections revealed metastatic carcinoma in ten of the thirty instances of breast carcinomas in which previous routine examination had not disclosed tumor in the nodes, i.e., in thirteen of the 149 lymph nodes. In some of these the tumor was readily evident and in one so extensive that it occupied approximately one-tenth of that particular section. Except for one instance, the tumor cells were first noted in the marginal sinus. From there they could be traced through subsequent sections. Frequently, the original tu-

The number of serial sections that revealed tumor varied considerably from lymph node to lymph node. In one instance only five sections disclosed carcinoma cells. The highest number of involved sections in one of the nodes was 190. No relationship could be established between the metastases and the morphologic degree of malignancy of the primary tumor.

Only one of the ten tumors was interpreted as a diffusely infiltrating carcinoma simplex, grade IV. Two were considered morphologically highly malignant, although they were not graded. Of the other seven, six were carcinoma simplex arising in the large ducts of the breast and one was a papilliferous cystadenocarcinoma. On the other hand, seven morphologically highly malignant tumors did not disclose metastases in the lymph nodes when cut serially.

From this study it is obvious that the routine laboratory examinations of axillary lymph nodes are inadequate to detect all metastases. One or two sections cut from each hemisected node often fail to present its true

status and, therefore, cannot be used as a basis for prognosis. Too, the histologic appearance of the primary tumor is often not characteristic enough to permit any conclusion as to the presence or absence of metas-

of lymph nodes of about even size, one might contain cancer cells and the others show only reticulum-cell hyperplasia. The consistency of the nodes may also be misleading. A number of the nodes with microscopic metastases

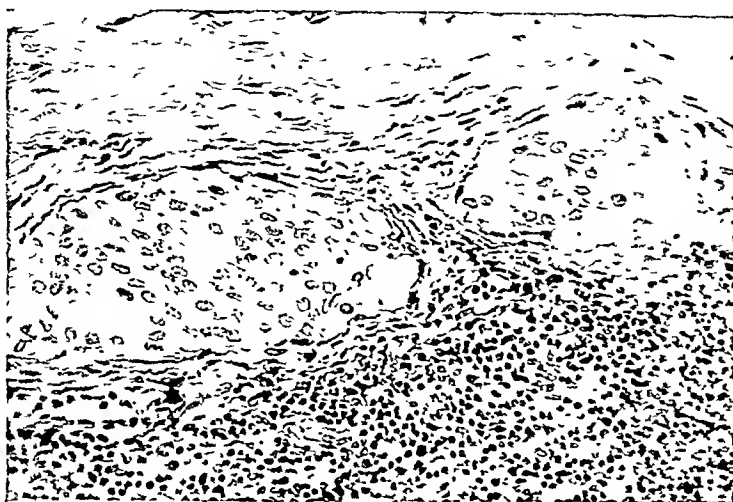


FIG. 3. Clumps of tumor cells in the marginal sinus of the lymph node. (Iron-hematoxylin-eosin preparation. $\times 225$.)

tases. Evidently it is impossible to determine the exact status of the patient with carcinoma of the breast, particularly the prognosis, unless adequate serial-section examinations have been made of the axillary lymph nodes. It might be mentioned in this connection that the time interval between the radical operation and this subsequent study, by serial sections, of the axillary lymph nodes was rather short, the longest interval being three years. One of these ten patients who had had a radical mastectomy three years ago had died two years later from generalized carcinomatosis. Another patient who had been operated upon one-and-a-half years ago shows clinical evidence of metastases in the lungs and spinal column. Seven other patients are apparently well. Data on the remaining one are not available.

No relationship could be established between the size of the node and the presence of tumor. In one instance of four lymph nodes the smallest, measuring 4 mm. in greatest diameter, was the only one that showed microscopic evidence of metastases. A number of nodes were considerably enlarged but did not contain tumor. In groups

were very soft and could, by touch, not be differentiated from those with reticulum-cell hyperplasia.

It is imperative therefore, that the surgeon remove as many lymph nodes as he can find, regardless of their size and consistency. After the specimen is received, the pathologist must seek out all lymph nodes. Each should be removed, cut in two and each half imbedded separately in such a fashion that the cut surface is sectioned first in one-half, and the peripheral surface in the other. Only serial sections cut from each half will show whether or not metastases are present. If this thoroughness is not feasible, as many sections as possible should be cut from each half of the node and examined.

During the examination of the lymph-node sections, attention was also paid to the possibility of recognizing changes that might precede metastases. Ewing maintained that lymph nodes in the vicinity of a carcinoma show progressive diffuse hyperplasia with catarrhal exfoliation of the sinus endothelium. In some instances there is an associated multiplication of lymphoid follicles. In others, the nodes are atrophic and fibrotic,

even extensively infiltrated with fat. He stated that such nodes may be by-passed by the tumor. Willis also described essentially similar changes and concluded that they were nonspecific. In studying the sections of the nodes we encountered changes similar to those described by Ewing and by Willis. As was mentioned before, many of the nodes that did not give evidence of metastases in serial sections were not only enlarged, but were considerably larger than normal. This was most commonly the result of a hyperplasia of the endothelial cells of the sinusoids, although reticulum-cell hyperplasia was also very frequent. In some instances hyperplasia of the lymph follicles alone was encountered. Austoni and also Guttner discussed preinvasive node changes which were seemingly characterized by endothelial and reticulum-cell hyperplasia. Parsons described similar changes in the lymph nodes throughout the body of mice after a local injection of a carcinogen. She also produced identical changes in the nodes after engrafting malignant tumors. Interestingly enough, some of these nodes produced tumor when transplanted into new animals. Parsons concluded that nodes seemingly free from metastases may contain some ultramicroscopic agent or carcinogen capable of producing tumors when transplanted. In view of our study, however, the question of whether or not serial sections

of the nodes would have brought metastatic tumor cells to light must be seriously considered.

From this study we must conclude that, in the absence of metastases, so-called preinvasive changes in lymph nodes draining a malignant tumor are nonspecific and not characteristic. There are no histologic criteria that indicate whether or not metastatic cancer cells may be found in the very next sections. There is nothing save examination of serial sections that will reveal early metastases in a given lymph node.

SUMMARY

Axillary lymph nodes from thirty patients with carcinoma of the breast, that on routine examination had been reported uninvolved, were restudied histologically by serial sections. Of these, ten, or 33.3 per cent, contained carcinoma cells. No relationship could be established between the presence or absence of metastases in the lymph nodes and a hyperplasia of the sinus endothelium or of the reticulum cells. The need to make more careful and through examinations of nodes in regions of malignant tumors is emphasized. The only means to rule out carcinomatous metastases is examination of serial sections. These are essential for a correct prognosis and evaluation of the results of surgery.

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A SYMPATHETIC GANGLIONEUROMA CULTIVATED IN VITRO

MARGARET R. MURRAY, PH.D., and ARTHUR PURDY STOUT, M.D.

A FEW years ago we were fortunate enough to obtain, in condition suitable for tissue culture, a biopsy from a localized, fully differentiated ganglioneuroma. A brief account of the case and tissue cultures is offered here, first because of their intrinsic interest from the standpoint of oncology, and second because it is now possible to relate these findings to a general survey of ganglioneuromas of the sympathetic nervous system,⁷ to studies of non-neoplastic adult sympathetic ganglia in vitro⁵ and of sympathicoblastomas in vitro.⁶

CASE HISTORY

A.M., was a Spanish girl, 9 years old. Two years before admission she had an attack of vomiting and fever. She was admitted to an-

other hospital, where a retroperitoneal tumor was felt and confirmed roentgenographically. Since then there have been no symptoms.

On examination in the Babies Hospital, New York, a firm, not freely movable abdominal mass was felt just to the left of the vertebral column in the lumbar region. Roentgenograms showed no relation to the kidney, but the left ureter was deviated laterally. An exploratory operation by Dr. William G. Hecks, March 3, 1942, revealed a tumor 12 × 10 cm. firmly attached to the posterior abdominal wall along the left lumbar vertebrae. It was considered inoperable and a biopsy specimen only was taken. Twenty-five months later the mass was still palpable and had not apparently increased in size.

From the Tissue Culture Division of the Laboratory of Surgical Pathology, Columbia University. Aided by the Marguerite Fischer Fund.

The authors wish to express their thanks to Mrs. Irene A. Pogocoff for technical assistance in the handling of the cultures, and to Mr. Walter O'Neill for the photography.

Received for publication, January 26, 1948.

Microscopic Examination. The report on paraffin sections of the specimen reads: This tumor is made up of widely scattered, adult, fully differentiated sympathetic ganglion cells with neurites and satellites, set in a fibrous stroma containing vast numbers of nonmedullated neurites sheathed by schwannian cells and endoneurium. The general arrangement of the nerve strands is that of a neurofibroma, and there are edematous microcystic areas of Schwann cells, characteristic of Antoni's B-

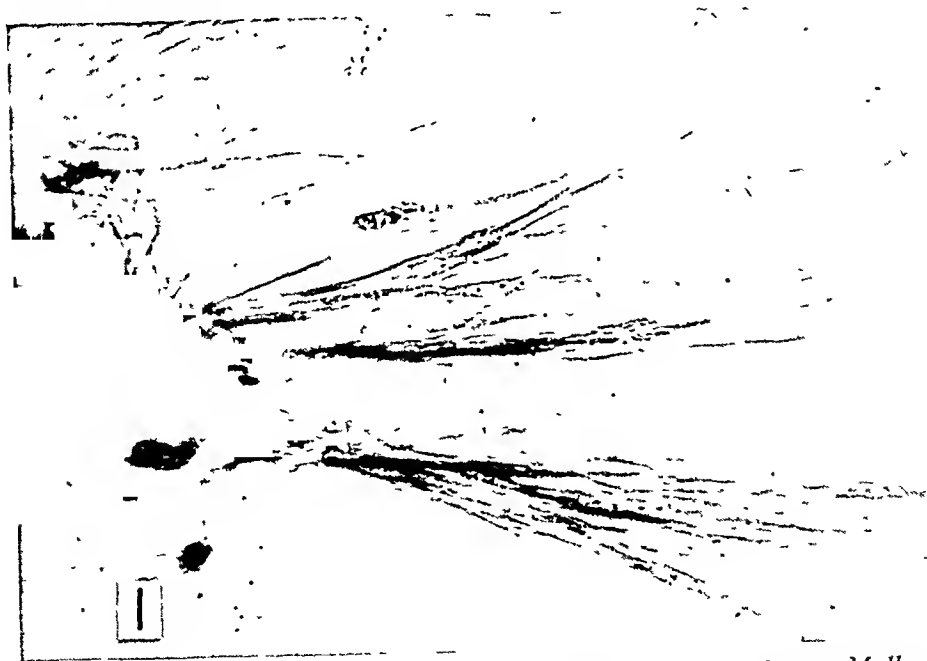


FIG. 1. A tuft of Schwann cells. Zenker's fixative, Masson-Mallory trichrome. Eighteen days in vitro. (× 420.)

typic tissue. The ganglion cells contain no melanin pigment. Their nuclei are usually eccentric; in some cells the nuclei are lobate, or multiple. A few pyknotic and degenerate ganglion cells are present.

Diagnosis. Localized, fully differentiated ganglioneuroma of lumbar peritoneal region (Stout,⁷ Case 4).

TISSUE CULTURE

Material from the biopsy specimen of the tumor was explanted according to an adaptation of the Maximow method described in a previous paper.⁴ Thirty explants were used and observations terminated after twenty-three days.

Filamentous outgrowths appeared at the edges of the cultures within three days after explantation. This is within the time-range for the first appearance of neurites from non-neoplastic sympathetic ganglion cells; but since ganglion cells were very sparsely scattered in this ganglioneuroma, it seems probable that the majority of the newly grown filaments were of schwannian origin. Within

seven days a number of ganglion cells had migrated clear of the explants, and within nine days very many tufts of vigorously growing Schwann cells could be identified with certainty. A transitory palisading of nuclei may appear in these bundles of Schwann cells at this time, but later, as the cell ribbons diverge in brush-formation in the unpopulated periphery of the clot, this regularity of arrangement is lost (Figs. 1, 5). Though mitoses are seen, the cells often have the appearance of dividing directly.

There is usually an area of marked fibrinolysis adjacent to the explant in the regions through which these schwannian tufts emerge (Fig. 5). Since this is not common in cultures of non-neoplastic Schwann cells,^{3,4} it may be that the Schwann cells entering into the ganglioneuroma should be regarded as neoplastic, even though they do not depart significantly from the normal in other respects. The microcystic areas seen in the sections, which are similar to those which characterize neurilemmomas, also contribute to this



FIG. 2 Ganglion cells (G) and Schwann or satellite cells (S). Zenker's fixative, phosphotungstic acid haematoxylin. Sixteen days in vitro. ($\times 400$.)



FIG. 3. A ganglion cell with many branching dendritic processes. Bouin's fixative, Bodian's protargol method of silver impregnation. Sixteen days in vitro. ($\times 460$.)

view. However, there were no frank (macrophage-like) B-cells evolved from the portion of the tumor used for tissue culture.

By eleven days after explantation the tufts of Schwann cells have increased in length and thickness, and more ganglion cells have emerged into the medium. At twenty-one days, as growth continues, fine reticulin fibers parallel to the Schwann cells can be demonstrated by McKinney's (1929) modification of the Bielschowsky silver technique.

Ganglion Cells. The ganglion cells that migrate out from the explants are generally enough like the non-neoplastic type to be easily recognized; they do, however, show a greater degree of variation from the norm. In general they develop more processes than the normal (Fig. 3), and these processes tend to run one upon another and become inextricably entangled. The cells do not keep their distance as is usual with ganglion cells, but sometimes overrun one another to form the semblance of a tissue (Figs. 6, 7). In these cultures the cell bodies and the neurites develop not only beads, but blebs (Fig. 3).

The emigrating neurons vary in size, but in general are smaller than the non-neoplastic cells from adults (Fig. 2). They exhibit many bizarre and lobated nuclei. Some cells are

binucleate (Fig. 4). During the third week of cultivation there were very many mitoses in the peripheral zone of the outgrowth, where ganglion cells may congregate in cultures of non-neoplastic ganglia; but though we frequently suspected that these mitoses were occurring in ganglion cells, we did not obtain conclusive evidence of it. Such evidence was found, however, in studies of ganglia from hypertensive individuals, where many more cultures could be followed.^{5, 6}

The Schwann cells and satellite cells often appear to be unusually rich in branches and variable in size, so that when the tendency of the ganglion cells to produce atypical nuclei is taken into consideration, it becomes difficult sometimes to be sure whether a given cell is neuron or satellite. In this ganglioma the proliferating elements appear to be mainly sheath cells and satellite cells (which are almost indistinguishable one from the other *in vitro*). Probably some ganglion cells also should be regarded as proliferating. The fibroblastic component of the nerve bundles is relatively inconspicuous in the cultures.

It was not possible to obtain a positive stain for Nissl substance with toluidine blue in these cultures. By this method some of the



FIG. 4. Ganglion cells and Schwann or satellite cells, cf. Fig. 2. Zenker's fixative, phosphotungstic acid haematoxylin. Sixteen days *in vitro*. ($\times 400$.)



FIG. 5. Tufts of Schwann cells, showing liquefaction area (L). Formalin fixation, Bodian's protargol method of silver impregnation. Twenty-one days in vitro. ($\times 186$.)

ganglion cells, and other cells as well, showed fine purple cytoplasmic granules, at the same time that the nuclear chromatin stained blue. In other cultures, stained by the Masson-Mallory trichrome technique, cytoplasmic granules which appeared similar to the above were colored by aniline blue.

When neutral red was applied supravitaly, the ganglion cells took up the stain in the form of round, rather uniform granules, either distributed through the cytoplasm or grouped together close to the nucleus. Non-neoplastic ganglion cells stained with neutral red present the same picture, and this was interpreted to mean that they might possess either the localized or the diffuse form of a Golgi apparatus.

DISCUSSION AND SUMMARY

The appearance and behavior in vitro of this fully differentiated ganglioneuroma is, as might be expected, essentially similar to

that of the non-neoplastic adult sympathetic ganglion and quite different from that of the sympathicoblastoma, an embryonic and malignant type of sympathetic neoplasm.

In addition to ganglion cells, the outgrowth of the ganglioneuroma contains many sheath and satellite cells, whereas none of the sympathicoblastomas of our experience has shown any glial elements at all. It is possible that sympathicoblasts represent a stage of neural development prior to the segregation of glia from neurones.

Though many of the ganglion cells depart from the normal picture in various ways, morphological differentiation generally appears to be complete in the sections of the tumor. In the cultures the cells tend to be small and to show more variation in form than those of non-neoplastic ganglia, but those that migrate appear no less differentiated on the whole. The absence of melanin pigment from this tumor may be of interest. According to Kuntz, melanin pigment is pres-



FIG. 6. *Matted processes of ganglion cells. Bouin's fixative, Bodian's protargol method of silver impregnation. Sixteen days in vitro. (X 230.)*



FIG. 7. *Ganglion cells with interlacing processes. Bouin's fixative, Bodian's protargol method of silver impregnation. Sixteen days in vitro. (X 460.)*

ent in the newborn and during the early years of life, but it rarely appears in abundance in the young except in association with pathological processes. Although the sympathetic ganglion cells of adults often contain considerable melanin pigment, we have found that the cells that migrate and divide in vitro rarely contain more than a few granules of melanin and most frequently none at all. It may be that physiological conditions favorable to multiplication of ganglion cells are relatively unfavorable to the accumulation of melanin.

The ganglion cells of this tumor do not form a true contiguous tissue in vitro, as is

the rule among sympathicoblasts. They do not, however, always remain entirely discrete and apart one from another like the non-neoplastic sympathetic ganglion cells; in some areas the processes of adjacent cells intertwine one with another to form a dendritic brush or mat. It is not possible to classify the processes of these cells as axons or dendrites, but it can be said that they are somewhat more numerous and more branching than those observed in cultures from non-neoplastic ganglia. This fact may contribute to the often described inequality in numbers between ganglion cells and neurites in these tumors.⁷

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AVAILABILITY OF GRANTS AND FELLOWSHIPS

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is entertaining applications for grants and fellowships. Applications for extension of existing Grants in Cancer Research will be received until October 1, applications for new grants until November 1. Final decision on applications submitted during this period will be made in most cases soon after February 1. Grants approved at this time ordinarily will become effective July 1, 1949.

Fellowship applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1 though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, Inc., on recommendation of the Committee on Growth, has approved research grants and fellowships totaling over \$2,000,000.

Communications regarding grants and fellowships should be addressed to Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D. C.

HISTOCHEMICAL STUDIES ON ABNORMAL GROWTH OF HUMAN ENDOMETRIUM

*I. Alkaline Phosphatase in Hyperplasia and Adenocarcinoma**†

WILLIAM B. ATKINSON, PH.D., and SAUL B. GUSBERG, M.D.

HISTOCHEMICAL studies have shown that endometrial alkaline phosphatase activity in the normal cyclic woman and hormone-treated ovariectomized monkey depends upon stimulation by estrogen.¹ It has been demonstrated that a high level of phosphatase activity is present in the surface and glandular epithelium of the estrogen-treated monkey and that subsequent treatment with progesterone results in a diminution of the enzyme. Similarly, the endometrial phosphatase activity is high during the proliferative phase of the human menstrual cycle, diminishes during the secretory phase, and disappears several days before the onset of menstruation.

In a recent histopathological study, Gusberg has presented evidence suggesting a correlation between prolonged estrogen stimulation and the development of endometrial hyperplasia and adenocarcinoma in women.

In view of the above findings, the present study was undertaken to determine histochemically the amount and distribution of alkaline phosphatase in hyperplasia and adenocarcinoma of human endometrium.

MATERIALS AND METHODS

The endometrial specimens included in the present investigation were obtained by curettage performed for diagnostic purposes at the Sloane Hospital for Women. A part of the tissue was fixed immediately in chilled (5-

10° C.) 80 per cent ethyl alcohol, the remainder in Zenker's fluid. The Zenker-fixed material was stained with hematoxylin and eosin for pathological survey. The tissue fixed in alcohol was dehydrated and imbedded in paraffin (56° C.) in the usual manner. Sections cut at 7 microns were incubated in a 1 per cent sodium glycerophosphate solution buffered at pH 9 according to the technique for the histochemical demonstration of alkaline phosphatase.² A slight modification was introduced by the addition of 0.01 M magnesium sulfate to enhance the enzyme activity. The incubation was carried out at 37° C. for one and one-half hours. The sites of phosphatase activity were made visible by subsequent treatment which results in the deposition of cobalt sulfide in small black particles. The sections were counterstained with eosin and were mounted in clarite dissolved in white gasoline.

OBSERVATIONS

Endometrial Hyperplasia. Sixteen cases of cystic glandular hyperplasia and four cases of adenomatous hyperplasia were studied. The patients ranged in age from 23 to 62 years; six of the women had passed the menopause. The presenting symptom in all cases was abnormal uterine bleeding.

Alkaline phosphatase activity was present in all cases irrespective of menopausal status. As in the normal cyclic endometrium, the enzyme was limited to the surface and glandular epithelium. In contrast to normal tissue, however, the degree of activity varied considerably from one gland to another (Fig. 1). In any individual specimen areas of marked activity may coexist with areas showing little or no phosphatase. The variation in enzyme activity appeared to be unrelated to the variation in glandular structure present

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* This investigation has been aided by a grant from the Jane Coffin Childs Fund for Medical Research and by a grant recommended to the American Cancer Society by the Committee on Growth of the National Research Council administered by Drs. Earl T. Engle and Howard C. Taylor, Jr.

† Read at the thirty-ninth annual meeting of the American Association for Cancer Research, Atlantic City, March 12, 1948.

Received for publication, April 2, 1948.

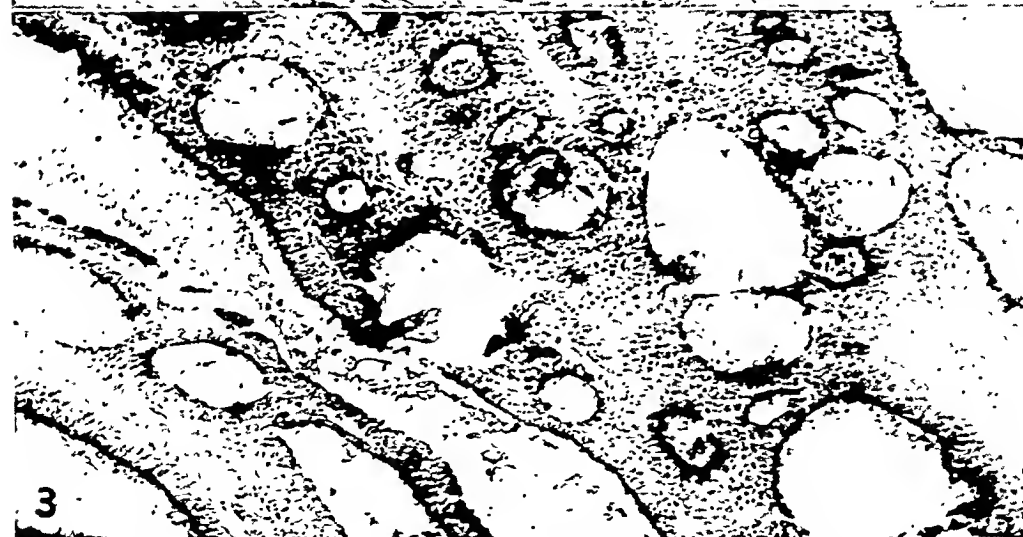


FIG. 1. Cystic glandular hyperplasia. Alkaline phosphatase deposition moderately intense but variable. ($\times 140$.) FIG. 2. Adenomatous hyperplasia. Alkaline phosphatase deposition moderately intense but variable. ($\times 140$.) FIG. 3. Adenocarcinoma—well differentiated. Alkaline phosphatase deposition moderate and variable. ($\times 140$.)

in all hyperplastic endometria, i.e., both normal-appearing and hyperplastic glands show all degrees of phosphatase activity. It is interesting to note that in glands containing alkaline phosphatase it was common to find the enzyme in the luminal secretion.

No discernable difference from the enzyme pattern just described was found in the cases of adenomatous hyperplasia studied (Fig. 2).

Endometrial Carcinoma. Twenty cases were studied in this group, the patients ranging in age from 33 to 67 years. Twelve women had passed the menopause. The tumors were divided into two groups on the basis of the usual pathological criteria of differentiation applied to adenocarcinoma.

DIFFERENTIATED CARCINOMA. Sixteen of these seventeen specimens exhibited alkaline phosphatase activity. As in hyperplasia, the activity is confined to the epithelial elements of the tumor and varied markedly in any single specimen from one area to another without reference to the degree of glandular differentiation (Fig. 3). In general this group gave the impression of reduced activity when compared with normal proliferative endometrium or the hyperplastic endometria described above. The findings were similar in tumors occurring in either pre- or postmenopausal women.

The single differentiated tumor that exhibited no glandular phosphatase activity was unique in that it was obtained from a very young woman and was associated with a late secretory endometrium.

UNDIFFERENTIATED CARCINOMA. All three specimens failed to show any significant alkaline phosphatase activity in the tumor cells (Fig. 4). Enzyme activity was present in the endothelium of the small blood vessels. This phenomenon, seen in all normal and pathological endometria, serves as an excellent technical control.

DISCUSSION

The opportunity to study the activity of alkaline phosphatase histochemically in a series of endometria with abnormal growth was of interest since it offered a demonstrable

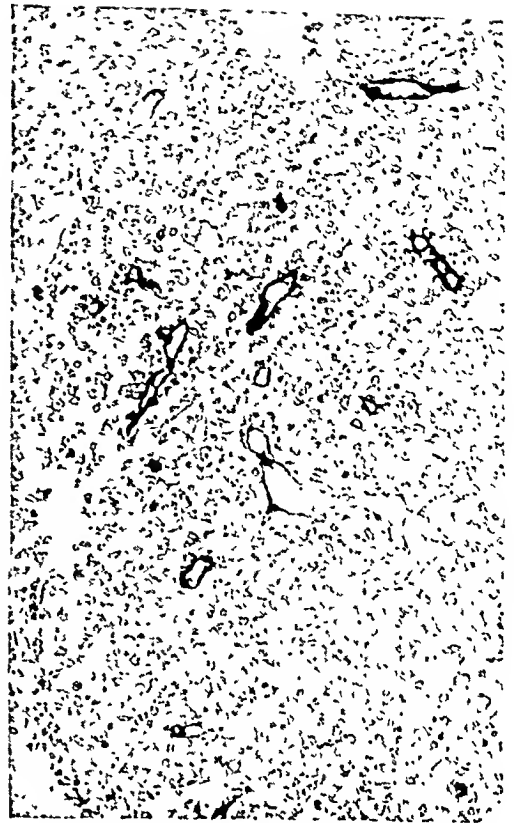


FIG. 4. *Adenocarcinoma, undifferentiated. Alkaline phosphatase absent in tumor cells. ($\times 140$.)*

tissue constituent that could be utilized in correlative studies of premalignant and malignant endometrial lesions.

The variation in enzyme activity in hyperplastic endometria is notable in that it resembles the histopathological observations of the variation and the focal activity in any endometrial hyperplasia. However, these variations in histological and enzymatic activity do not coincide in the tissue. It is interesting to note the presence of alkaline phosphatase in all hyperplastic specimens, even those obtained from women long past the menopause. One may speculate on the role of estrogenic stimulation in the development of these late hyperplasias and also on possible sources of such estrogen. However, we have not undertaken any metabolic studies of estrogen secretion to attempt correlation with the reported tissue activities.

The inverse relationship between alkaline phosphatase activity and histological tumor activity suggests that this enzyme picture is not a simple manifestation of growth. It is

significant that the greater the differentiation, the greater is tumor participation in normal environmental phenomena, whereas anaplastic adenocarcinomas no longer appear to respond with respect to this enzyme. The analogy to the endocrine-enzyme-tumor relationship in the prostate appears close.

The role of estrogen in the development of endometrial carcinoma has not been conclusively demonstrated although it has been suggested by clinical observations. One may think of endometrial alkaline phosphatase as a possible indicator of such endocrine activity, but the proof of this hypothesis lies beyond the scope of this present work. It is possible that the histochemical demonstration of alkaline phosphatase in these endometrial growth abnormalities may be related to other metabolic activities of these tumors that are without steroid significance.

SUMMARY

Alkaline phosphatase activity has been studied histochemically in a series of hyperplastic and carcinomatous human endometria. The enzyme has been found in all cases of hyperplasia, the amount and distribution varying without relation to either the degree of hyperplasia or the menopausal status of the patient. On the other hand, in adenocarcinoma, a definite inverse relationship exists between the degree of tumor activity, as judged by the usual histopathological criteria, and the over-all phosphatase activity. In undifferentiated carcinomas the tumor cells contain little or no enzyme; as in hyperplasias, differentiated tumors exhibit variable phosphatase activity that is unrelated to either the morphological patterns within the individual tumor or the menopausal status of the patient.

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THE DISTRIBUTION OF RADIOACTIVITY IN THE MOUSE FOLLOWING ADMINISTRATION OF DIBENZANTHRACENE LABELED IN THE 9 AND 10 POSITIONS WITH CARBON 14*

CHARLES HEIDELBERGER, PH.D., and HARDIN B. JONES, PH.D.

EVER since the demonstration in 1930 by Kennaway and Hieger that 1, 2, 5, 6-dibenzanthracene, a pure chemical compound, is capable of producing cancer, there has been a great deal of interest and work in the field of chemical carcinogenesis. The isolation and characterization of 3, 4-benzpyrene as one of the carcinogenic agents of coal tar by Hieger¹³ and by Cook and Hewett, in 1933, stands as one of the milestones in this field, and tied in the researches on occupational skin cancers with the ever-increasing activity in the study of the carcinogenic hydrocarbons. This work was carried on chiefly by Cook and Kennaway in England and Ficser and Shear in America, by whom a very large number of related compounds were synthesized and tested for carcinogenic activity. As the synthetic activity was at its height, a series of investigations were launched with the aim of elucidating the mode of action of these substances. This work has mostly been concerned with the three compounds, 1, 2, 5, 6-dibenzanthracene, 3, 4-benzpyrene, and 20-methylcholanthrene, and centered about studies of the distribution, metabolism, and effect of these substances on the biochemical and physiological environment of the cell, epidermis, and the animal as a whole.

The analytical technique that has been em-

ployed in the researches on the distribution and metabolism of these carcinogens makes use of their characteristic fluorescence or absorption of ultraviolet light. It is this fluorescence that made possible the isolation of benzpyrene from coal tar. In the case of dibenzanthracene, the compound with which we are concerned in the present work, Berenblum and Kendal¹ and Chalmers⁷ in 1934 found that after a few weeks, no carcinogen could be detected at the site of injection into the breast muscle of fowls. Hieger,¹⁴ in 1936, showed that dibenzanthracene administered subcutaneously to rats was retained for longer periods at the site of injection, whereas Berenblum and Kendal² demonstrated that there was a more rapid disappearance after intraperitoneal administration and were unable to detect any carcinogen in the feces. In the same year, Chalmers and Peacock showed that a distinct fluorescence could be detected in the bile of mice following the intravenous injection of an aqueous colloid of methylcholanthrene and benzpyrene, whereas no such effect was observed with dibenzanthracene. Lorenz and Shear were able to detect an appreciable quantity of dibenzanthracene in tumors produced six months after a single subcutaneous injection in lard.

In 1937, a significant advance in the knowledge of the metabolism of dibenzanthracene was made when Levi and Boyland reported the isolation from rabbit excreta of a compound that they characterized as being a dihydroxydibenzanthracene; in 1939 Dobriner, Rhoads, and Lavin^{10, 11} isolated a different dihydroxy compound from the urine and feces of rats and mice. This latter compound was shown by the synthesis of Cason and Fieser to be 4', 8'-dihydroxydibenzanthracene. It is of interest to note that several

Department of Chemistry, Division of Medical Physics, and the Radiation Laboratory, University of California, Berkeley, California.

* This paper is based on work performed under Contract #W-7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley, California. Preliminary reports of this work were presented at the meeting of the American Association for Cancer Research, Inc. in Chicago, May, 1947, at the Fourth International Cancer Congress, St. Louis, Sept., 1947, and at the 50th anniversary meeting of the Columbus Section of the American Chemical Society, October, 1947.

Received for publication, February 26, 1948.

phenolic metabolites of benzpyrene have been isolated and characterized.

R. N. Jones and Jones, Dunlap, and Gogek have made careful attempts, using ultraviolet spectroscopy as their analytical tool, to obtain a complete balance of elimination and retention of dibenzanthracene and its phenolic metabolite following subcutaneous and intraperitoneal administration. However, they were usually able to account for only about one-third of the dose. Since only the intact pentacyclic aromatic ring system gives the characteristic fluorescence and ultraviolet absorption, it has been concluded by all workers in this field that there must be some more deep-seated degradation that occurs in the body to account for the complete disappearance of most of the carcinogen following various modes of administration.

With the availability from the U. S. Atomic Energy Commission of the long-lived radioactive isotope of carbon, we decided to undertake a reinvestigation of the distribution and metabolism of a carcinogenic hydrocarbon. It was hoped that a suitably labeled compound could be traced by following the radioactivity through the mouse, that this could be done with greater simplicity and accuracy than by the optical methods, that quantitative recoveries might be made, and that hitherto unknown metabolites might be discovered. All of these hopes have now been realized.

Dibenzanthracene was the compound chosen for this investigation because a suitable synthesis was available, because a considerable body of data on its metabolic behavior was already in the literature, and because it is a symmetrical molecule that can be labeled in a symmetrical position, which might simplify the problem of identifying unknown metabolites. Accordingly, the synthesis of dibenzanthracene labeled in the 9 and 10 positions with C14 was carried out by Heidelberg, Brewer, and Dauben.

APPARATUS AND METHODS

Each mouse was injected with a known amount of dibenzanthracene and placed in a metabolism cage for the duration of the experiment. The cage was swept with a con-

tinuous stream of air that was bubbled through a tower filled with sodium-hydroxide solution to trap expired carbon dioxide. Urine and feces were collected at periodic intervals, and at the appropriate time the mouse was sacrificed and dissected. The cage was washed with benzene and water. The specimens were kept frozen until assayed for radioactivity.

The respiratory carbon dioxide was precipitated as barium carbonate, filtered, dried, weighed, plated, and counted with a thin mica-window Geiger-Müller counter according to the method of Dauben, Reid, and Yankwich. An aliquot of the urine specimens was plated and counted directly, and checked occasionally by combustion. The feces and the tissue or organ samples were burned in oxygen in a standard organic combustion train. The carbon dioxide was absorbed in sodium hydroxide, which was treated as described for the respiratory carbon dioxide. These samples were burned without drying in order to avoid the loss of volatile organic substances, and because adequate sampling is impossible under these conditions, the entire specimen was combusted in all cases. The total radioactivity of each sample was determined in this way, and was calculated as a percentage of the activity in the initial dose. The over-all error in each determination is less than 5 per cent and radioactivity corresponding to 1 gamma of dibenzanthracene can be determined with this accuracy.

In those experiments in which the total recovery of radioactivity was low, it is believed that the loss occurs by leakage from injection sites and from small accumulated errors in individual assays, rather than from gross errors or losses during the assays.*

DISTRIBUTION OF RADIOACTIVITY

Following Intravenous Injection. The dibenzanthracene was administered intravenously as an aqueous colloid, 1 ml. being injected into the tail vein of each mouse. It was prepared as follows: 0.5 mg. of diben-

* For these analyses we are deeply indebted to Mrs. Sally Brown, Mrs. Martha Kirk, Mrs. Mary Spilman, Mrs. Marion Perkins, Miss Mary Lee, Mrs. Beverly Dandliker, Mrs. Yvonne Stone, and Miss Martha Landefeld.

zanthracene is dissolved in 0.3 ml. of redistilled acetone, and this solution rapidly pipetted through a very fine orifice under the surface of 1 ml. of water in a centrifuge tube. A very finely dispersed colloid is formed; the acetone is removed by bubbling a stream of air through the mixture, which is then made isotonic with 20 mg. of glucose. The colloid prepared in this way is usually stable for several days.

Table 1 summarizes the data obtained

any excretion is small compared with the amount found in the feces. In one mouse, a large mammary carcinoma, already present, took up a small amount of radioactivity, but this was considerably less than was found in the liver. However, it is evident that by this mode of administration there is little absorption of dibenzanthracene into the system, but that it is rapidly eliminated.

Table 2 shows that there is an extremely rapid initial uptake of the colloidal substance

TABLE 1
RECOVERY OF DIBENZANTHRACENE

	Experiment 3 Strain A mouse ♂ wt. 17 gm. 0.42 mg. colloid given intravenously 24 hrs.			Experiment 5 Strain A mouse ♂ wt. 27.6 gm. 0.341 mg. colloid given intravenously 48 hrs.		
	Wt. wet tissue	Total counts/ min.	% of dose	Wt. wet tissue	Total counts/ min.	% of dose
Dose		28,300			22,800	
Respiratory carbon dioxide	11.908	15	0.05	19.19	<100	<0.4
Urine		92	0.32		1770	7.76
Feces		1590	5.62		9150	40.0
Gastrointestinal tract and contents						
Liver	2.432	25,200	88.7	2.643	3330	14.6
Salivary glands	1.197	975	3.47	1.718	2610	11.4
Lymph nodes	0.078	73	0.26	0.053	196	0.86
Spleen	0.017	0	0	0.105	96	0.42
Seminal vesicles	0.128	0	0	0.261	0	0
Body fat	0.278	0	0	0.159	0	0
Skin and hair	0.155	0	0	0.288	0	0
Muscle	2.792	0	0	3.274	0	0
Bones	1.008	0	0	2.002	0	0
Brain	4.494	0	0	5.602	0	0
Lungs	0.364	0	0	0.392	0	0
Blood plasma	0.101	104	0.37	0.155	87	0.38
Blood cells	0.296	88	0.31	0.181	130	0.57
Kidneys	0.226	0	0	0.252	0	0
Heart	0.223	0	0	0.348	130	0.57
Mammary carcinoma	0.080	0	0	0.101	452	1.98
TOTAL RECOVERY		28,100	98.8	2.767	1180	4.90
					19,300	84.5

from mice sacrificed twenty-four and forty-eight hours after intravenous administration of the dibenzanthracene colloid. Essentially a quantitative recovery of the dose has been found, in contrast to all previous work. This indicates that degradation products, if formed, are detected by their radioactivity, whereas fluorescence or ultraviolet absorption spectra are not adequate for this purpose.

There is an insignificant amount of radioactivity in the respiratory carbon dioxide; most of the activity is found either in the feces or the gastrointestinal tract. The urin-

TABLE 2
INITIAL STEPS IN DISTRIBUTION

	0.5 Mg. of Aqueous DBA Colloid Injected Intravenously		
	% of dose		
	½ hr.	1½ hr.	24 hr.
Liver	89.	82.	3.5
Spleen	1.9	2.3	0
Plasma	0.24	0.10	0
Red cells	1.00	0.71	0
Intestinal contents and feces	1.9	7.6	94.
Lungs	0.43	0	0.37
TOTAL RECOVERY	94.7	97.0	98.8

by the liver and the early appearance of activity in the intestinal contents. There is a measurable blood level in the early period, and the activity is more closely associated with the red cells than with the plasma, which may be a surface adsorption phenomenon since the material is in colloidal form. The presence of radioactivity in the lungs is in accord with the observations of Lorenz and Shimkin made with methylcholanthrene, and may explain the induction of pulmonary tumors following repeated intravenous injections of these carcinogens.

It seemed reasonable that the elimination must occur through the bile, although Chalmers and Peacock failed to detect any fluorescence in the bile of mice after intravenous administration of dibenzanthracene colloids. A bile fistula was performed on a mouse through which a glass cannula was inserted into the bile duct; this was then tied off so that all of the bile was removed and collected. Mice so treated live for about twenty-four hours. Table 3 shows strikingly that fecal elimination following intravenous adminis-

TABLE 3
BILE DATA FROM INTRAVENOUSLY
INJECTED COLLOID

	% Total Activity Given, 24 Hours	
	Normal Mouse	Bile-Fistula Mouse
Feces	5.62	0
Stomach & contents	4.15	0
Intestines	0	0
Intestinal contents	48.30	0
Bile	none	53.2
TOTAL	58.1	53.2

tration of dibenzanthracene colloid takes place exclusively through the bile.

Following Administration by Stomach Tube. Table 4 shows the distribution of activity twenty-four and forty-eight hours after administration of dibenzanthracene as an aqueous colloid and also dissolved in tri-caprylin. Each mouse was dissected and burned completely, as shown in Table 1, but the only organs listed here are those containing significant amounts of activity.

TABLE 4
ADMINISTRATION BY STOMACH TUBE

Experiment 7 A strain mouse ♂ wt. 28.5 gm. 0.517 mg. in tricaprylin 24 hrs.				Experiment 29 A strain mouse ♂ wt. 35 gm. 0.452 mg. in tricaprylin 48 hrs.			
	Wet weight	Counts/min.	% of dose		Wet weight	Counts/min.	% of dose
Dose		34,600				30,300	
Urine		556	1.66			1,310	4.32
Feces		13,800	39.9			22,500	74.4
Liver							
Stomach and contents	2.490				0.376	79	0.26
Intestines		17,200			1.052	0	0
Intestinal contents	1.745	1,150	50.0		1.204	0	0
RECOVERY		32,700	3.32		1.558	0	0
			94.9			23,900	79.0

Experiment 8 A strain mouse ♂ wt. 18.3 gm. 0.530 mg. in colloid 24 hrs.				Experiment 27 A strain mouse ♂ wt. 33.5 gm. 0.380 mg. in colloid 48 hrs.			
	Wet weight	Counts/min.	% of dose		Wet weight	Counts/min.	% of dose
Dose		35,500				25,400	
Urine		17,100	48.8			580	2.3
Feces						20,600	81.0
Liver							
Stomach and contents	0.299	5,360	15.1		0.449	220	0.9
Intestines		1,064	3.00		1.273	0	0
Intestinal contents	1.568	5,170	14.5		2.159	0	0
RECOVERY		0	0		1.766	0	0
	1.087		81.4			21,400	84.2

It is plain that the radioactive substances are eliminated almost exclusively in the feces, so rapidly that there is no detectable activity in the intestines and intestinal contents forty-eight hours after administration. There seems to be little difference in the fate of the dibenzanthracene whether administered as a colloid or in tricaprylin, and there is no evi-

each mouse was dissected completely, but only the organs containing significant amounts of radioactivity are listed. Figure 1 shows the rate of elimination of activity in the feces. The dotted line represents one mouse, and the solid line, another. The rates are entirely self-consistent for each individual mouse, but there is a difference in the elimin-

TABLE 5
INTRAPERITONEAL INJECTION

Each Mouse Received 1.0 mg. of Dibenzanthracene in 0.30 cc. Tricaprylin						
	% of dose					
	1½	1½ fistula	2	3	6	7 (days)
Total urine eliminated	0	0	1.26	0.85	1.14	3.9
Total feces eliminated	0	0	8.6	24.2	35.6	74.
Contents of peritoneal cavity	70.5	63.2	39.3	32.2	25.4	11.8
Stomach and contents	0.46	0.63	0.46	1.82	0.48	0.89
Intestines	1.77	2.9	2.9	4.04	6.9	5.6
Intestinal contents	5.45	7.5	5.1	6.9	2.6	0.85
Liver	0	2.5	2.2	3.9	5.5	4.5
Body fat	5.2	0.63	3.6	3.4	1.9	1.1
Kidneys	0.36	0.16	0.67	0.41	0.36	0
Carcass	0.24	0	0	5.4	7.4	9.3
RECOVERY	86.	83.	70.	87.	100.	108.

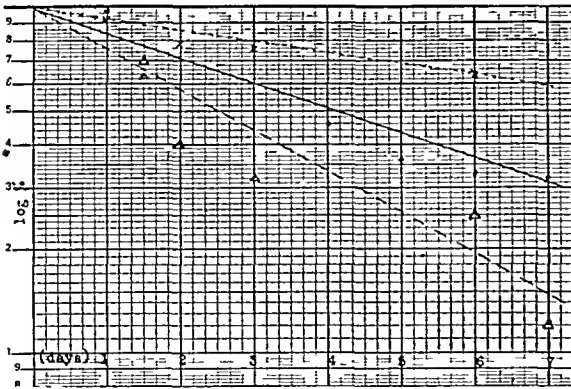
dence, aside from small amounts of activity in the liver and urines, that any appreciable quantity of material is absorbed into the body following this mode of administration.

Following Intraperitoneal Injection. The results of a series of mice injected intraperitoneally with a solution of dibenzanthracene in tricaprylin is shown in Table 5. Again,

ation rates of the two mice. The dashed line represents the retention of radioactivity in the peritoneal cavity, and on this curve each point represents a different mouse, but again within the limits of individual variation, the results are consistent. This figure also shows that the activity disappears from the peritoneal cavity at a faster rate than it is eliminated in the feces.

A mouse with a bile fistula was given an intraperitoneal injection of dibenzanthracene. As Table 6 shows, there is a much smaller amount of activity found in the bile by this mode of administration than by the intravenous route, and this biliary elimination represents only a relatively unimportant proportion of the total fecal elimination.

Our data on retention in the body are in qualitative agreement with those of Berenblum and Kendal,² but whereas they were unable to detect any fluorescence in the feces, we find these to be the principal route of elimination of radioactivity from the peritoneal cavity. The detection of activity in the carcass (a term which includes all parts of the mouse not otherwise specifically mentioned in Table 5) is in agreement with the results of Jones, Dunlap, and Gogek, who



× . . . Accumulated amount of elimination in feces, mouse A.
• . . . Accumulated amount of elimination in feces, mouse B.
△ . . . Retention in peritoneal cavity, 6 mice.
FIG. 1. Elimination in mice injected intraperitoneally with 1 mg. dibenzanthracene in tricaprylin.

TABLE 6

BILE DATA FROM INTRAPERITONEAL INJECTION IN TRICAPRYLIN

	% Total activity given 18 hrs.
Feces	none
Stomach and contents	0.63
Intestines	2.9
Intestinal contents	7.5
Bile	0.36
TOTAL	11.4

found an appreciable quantity of dibenzanthracene in the carcass fourteen days after intraperitoneal injection in tricaprylin.

A comparison of the intestines and the intestinal contents shows that, at first, there is more radioactivity in the contents than in the intestines themselves, whereas by the sixth day there is more activity in the intestines than in the contents. Since the weights involved are approximately the same, the values of total radioactivity are roughly proportional to the specific activities. This observation suggests the possibility that the radio-carbon compounds are eliminated in the feces by direct passage across the intestinal walls, and that absorption into the rest of the body takes place through the intestines. At present, however, there is not sufficient evidence to permit any definite conclusions to be drawn about the actual mechanism of absorption or elimination following this mode of administration.

RETENTION OF RADIOACTIVITY

Following Subcutaneous Injection. There is considerable evidence that dibenzanthracene is retained for fairly long periods at the site of subcutaneous injection in fatty solvents. R. N. Jones found 36 per cent of the dibenzanthracene injected subcutaneously in olive oil after eight weekly injections to two rats, and Hieger¹⁴ showed qualitatively that dibenzanthracenes administered in lard to rats was detectable for various periods of time after injection, depending on the dose. Borenblum and Shoental have shown that the rate of elimination of benzpyrene from the mouse following a single subcutaneous injection in sesame oil is constant.

We have given a series of mice a single subcutaneous injection of dibenzanthracene in tricaprylin, have sacrificed them periodically and burned and assayed the entire region of the site of injection. The results showing the rate of disappearance from the site are shown in Fig. 2. They indicate a

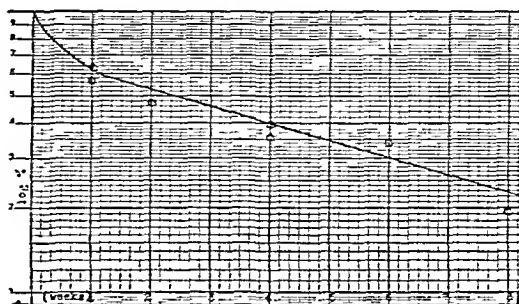


FIG. 2. Rate of disappearance from site of subcutaneous injection in tricaprylin.

fairly rapid elimination during the first week, after which a constant slower rate is maintained. Each point of the curve represents a single mouse, and there is relatively little individual variation.

The feces of one mouse were collected during the first week following subcutaneous injection; the results shown in Fig. 3 indicate

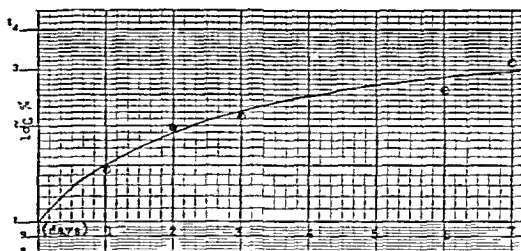


FIG. 3. Accumulated elimination in feces from subcutaneous injection in tricaprylin.

that again fecal elimination is the means of removal of dibenzanthracene from the mouse. There appears to be a more rapid elimination during the first two days, and then a steady rate is maintained. In this mouse 57 per cent of the radioactivity remained at the site, and hence the total recovery in this experiment is 89 per cent. This is in qualitative agreement with R. N. Jones who has detected small amounts of dibenzanthracene in

the feces of rats that had received massive subcutaneous doses of dibenzanthracene.

Retention in Tumors Produced by Dibenzanthracene. In an important investigation, Lorenz and Shear showed that tumors produced six to eight months after a subcutaneous injection of dibenzanthracene in lard still contained substantial quantities of dibenzanthracene.

To date, we have obtained six tumors that were produced by single subcutaneous injections of the radiodibenzanthracene dissolved in either tricapyrylin or mouse fat. These tumors were dissected when large, were homogenized, and an aliquot assayed for radioactivity. Table 7 shows the results obtained.

been expressed as radioactivities. This radioactivity was introduced into the mouse in the 9 and 10 carbon atoms of dibenzanthracene, but the assays only show the presence of these labeled carbon atoms and give no information whatever about the compounds into which they are incorporated. There is absolutely no justification to assume that the radioactivities obtained in this study represent unchanged dibenzanthracene; they merely show the presence of the carbon atoms originally situated in the carcinogen—these may be in completely different compounds by the time the assays are made.

It must also be emphasized that our results are in no way contradictory to the earlier

TABLE 7
RADIOACTIVITY IN TUMORS PRODUCED BY DIBENZANTHRACENE

Time (mos.)	Solvent	Tumor	Cts/min.	%
6	Mouse fat	Spindle-cell sarcoma	1250	3.7
10	Mouse fat	Spindle-cell sarcoma	980	2.9
4½	Tricaprylin	Hyperkeratosis of the skin with early squamous-cell carcinoma	1460	5.75
6	Tricaprylin	Hyperkeratosis of skin with early subcutaneous spindle-cell sarcoma	745	1.2
6	Tricaprylin	Spindle-cell sarcoma	5700	9.25
8	Tricaprylin	Spindle-cell sarcoma with marked hyalinization	4000	7.8

There is considerable variation among individual mice, and the activity retained depends upon the solvent used, but in every case there is an appreciable amount of activity present. The lower of the values obtained from the tricapyrylin experiments corresponds fairly closely with those predicted by extrapolation of the curve in Fig. 2. The higher values do not seem beyond the range of the individual variations that one might expect in that curve. There is no evidence to suggest any difference between the rate of incidence of tumors in these experiments and in the controls, which were given equivalent doses of nonradioactive dibenzanthracene.*

DISCUSSION OF RESULTS

In the foregoing discussion all results have

work done in this field. In these previous investigations the only available analytical techniques were fluorescence and ultraviolet spectroscopy, which in order to show the connection, require the presence of the polycyclic hydrocarbon ring system in essentially unaltered form. The very low quantitative recoveries of dibenzanthracene and dihydroxydibenzanthracene administered under a variety of conditions have always been correctly interpreted^{1, 2, 3, 5, 6, 10, 14, 15, 16} as meaning that some deep-seated alteration of the molecule has taken place during its metabolic course. The fact that we obtain essentially quantitative recoveries of the administered dose does not in any way imply superior technique, but only that the analytical tool that we have used permits the tracing of any and all substances originally derived from the dibenzanthracene containing the labeled carbon atom, is capable of higher precision, and is free from such errors as those introduced by light-absorbing substances

* We are greatly indebted to Dr. Michael Shimkin and Dr. Isabella Perry for the histological examination of these tumors. They report that none was markedly different from the usual tumors induced by subcutaneous injection of dibenzanthracene.²¹

present in the tissues. The evidence for the metabolic degradation of dibenzanthracene, together with some of the chemical characteristics of these metabolites, will be presented in the accompanying paper.

The absence of radioactivity in the carbon dioxide of respiration is clear proof that the dibenzanthracene is not metabolized in such a way that the 9 and 10 carbon atoms appear in any of the common biochemical intermediary metabolites (acetate, pyruvate, citrate, glucose, etc.), since these substances are known to be very rapidly oxidized; if they were present even in minute amounts, there would be an appreciable radioactivity in the respiratory carbon dioxide.

The results we have obtained show that in general the carcinogen is eliminated as rapidly from the body as each mode of administration will permit, and that relatively little is absorbed into the body. The major route of elimination in all cases is through the feces; urinary excretion is of relatively minor importance. As nearly as can be deduced from the evidence now at hand, the mouse treats the carcinogen as a toxic substance and handles it pretty much as would be physiologically expected depending on the mode of administration. In the process of elimination, the compound is drastically degraded, possibly as a detoxication mechanism. There is no apparent tendency for the substance to concentrate within a short period of time in neoplasms already present in the animal.

Although there are no noticeable effects from the radiation of the labeled carcinogen, it seemed desirable to attempt to calculate their radiation dose in an experiment. For this we have chosen the case of a subcutaneous injection in tricapyrylin, in which the substance remains at the same site over relatively long periods of time.

Calculation of the Irradiation Dose in the Tissue Immediately Surrounding a Subcutaneous Injection of 1 mg. of Dibenzanthracene in 0.3 cc. of Tricapyrylin.

sp. act. of dibenzanthracene = 67,000 cts/min./mg. = 1.14×10^6 dis./min.
average energy of C14 beta = 0.050 Mev.
 1.14×10^6 dis./min. $\times 5 \times 10^6$ ev./dis. $\times 1.6 \times 10^{-12}$ ergs/ev. = 9.1×10^{-2} ergs/min.
1 day = 1440 minutes
So the intensity of radiation from the DBA is 1.31×10^2 ergs/day

Now there are 0.083 ergs/mg. of tissue/r
 $r = \beta$ — roentgen equivalent
So the total possible intensity of radiation
 $= \frac{1.3 \times 10^2}{0.083} = 1570$ r/day

Consider the drop of tricapyrylin subcutaneously as a sphere

Volume = 0.3 cm.³ Radius = 0.42 cm.

Surface area = 2.2 cm.²

The $\frac{1}{2}$ absorption thickness of β of C14 = 0.0025 cm.

and the half range is 0.013 cm.

Let us calculate the amount of irradiation received by the tissue of $\frac{1}{2}$ thickness immediately surrounding the sphere of tricapyrylin.

The effective radiation can only come from the depth of the range of the C14 beta ray, and under these conditions 90% of the radiation is lost by self-absorption, and hence 10% is effective.

$0.420 - 0.026 = 0.394$ = radius of sphere — whole range

$V = \frac{4}{3} \pi (0.394)^3 = 0.255$ cm.³

Volume of irradiating segment = 0.300 — 0.255 = 0.045 cm.³

Surface area $\times \frac{1}{2}$ thickness = 0.0055 cm.² = 5.5 mg. of tissue immediately surrounding the sphere that is receiving $\frac{1}{2}$ of the radiation. $\frac{1}{2}$ is the directional factor.

Dose =

$$\frac{\frac{1}{2} \text{ Intensity} \times \text{effective radiation} \times \text{irradiating volume}}{\text{wt. of tissue} \times \text{total volume}} = \frac{1570 \times 0.1 \times 0.45}{5.5 \times 0.300 \times 2} = 2.1 \text{ r/day}$$

Thus the total irradiation received by the tissue immediately surrounding the droplet, as calculated from Fig. 2:

1 day	2.1 r
7 day	10.0 r
35 day	47.0 r
180 day	83.0 r
∞ day	84.0 r

For comparison, in tracer experiments with radioactive phosphorus, a single mouse is regularly given doses of 16 r/day or 140 r in twenty days over the entire body, with no perceptible biochemical or other changes. If one considers the relative weights involved in the comparison, it will be seen that in the latter case the mouse is receiving, with no observable effects, a total irradiation of about 7000 times that of the dibenzanthracene mouse.

SUMMARY

Dibenzanthracene, labeled in the 9 and 10 positions with C14, has been administered to mice intravenously and by stomach tube as an aqueous colloid, and intraperitoneally, subcutaneously, and by stomach tube in tricapyrylin solution.

The distribution of radioactivity in the

mice at various time intervals after administration of the carcinogen has been determined.

The radioactive substances are rapidly eliminated, largely through the feces, and ordinarily very little material is absorbed. The distribution and rate of elimination depends

upon the mode of administration.

There is an appreciable quantity of radioactivity in tumors produced several months after a single subcutaneous injection of dibenzanthracene.

There appear to be no detectable effects from the irradiation of the labeled carcinogen.

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THE METABOLIC DEGRADATION IN THE MOUSE OF DIBENZANTHRACENE LABELED IN THE 9 AND 10 POSITIONS WITH CARBON 14^{*}

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IN the accompanying paper,¹⁰ studies of the distribution of radioactivity following the administration of dibenzanthracene labeled in the 9 and 10 positions with C¹⁴ have been described. In contrast to all earlier reports, a virtually quantitative recovery of the dose administered has been accomplished. This is because all substances derived from the carcinogen and still containing the labeled carbon atoms may be traced by following the radioactivity, whereas the spectroscopic or fluorometric methods of analysis previously used are capable of directly detecting only those metabolites that maintain the intact pentacyclic aromatic ring system. This non-quantitative recovery of carcinogen and apparent disappearance have always been interpreted ^{4, 7, 11} as being due to metabolic degradation of the compound to other substances with noncharacteristic absorption spectra or fluorescence. Levi and Boyland in 1937 reported the isolation of a dihydroxydibenzanthracene from rabbit urine, and Dobriner, Rhoads, and Lavin, in an extremely thorough study of the excreta of various animals given dibenzanthracene subcutaneously, isolated another compound from the urine and feces of rats and mice, which was proved to be 4', 8'-dihydroxydibenzanthracene. In spite of a very extensive fractionation of excreta,

bile, intestinal contents, and whole mice, these investigators were unable to detect any other absorption spectra that appeared to be derived from the administered dibenzanthracene. Yet only a small percentage of the original material could be accounted for.

It was decided to reinvestigate the problem of metabolic degradation using the radioactive carcinogen. Since it has been shown¹⁰ that most of the radioactivity is found in the excreta, a systematic study was undertaken in order to gain some information about the types of substances produced as degradation products, and to contrast and compare the patterns of metabolism of the dibenzanthracene when administered by different routes. Accordingly, we have submitted to chemical fractionation urines, feces, biles, subcutaneous injection sites, and tumors produced by the labeled carcinogen chemically. In these fractionations the radioactivity was determined in each step, and it was found immediately that the compound is degraded to several substances, some highly water-soluble that are chemically very different from the original material, and must involve some deep-seated changes in the molecule. It is not surprising, then, that spectroscopic methods failed to detect these substances, for even if new bands were observed there could be no definite demonstration that these originated from metabolites of dibenzanthracene.

Water-soluble derivatives of dibenzanthracene have been reported as having been obtained by photochemical oxidation of the compound in benzene solution. Boyland and Boyland in 1934 studied the effect of these substances on various enzyme systems, and Allsopp and Szigeti have determined their absorption spectra and tested them for carcinogenicity. We have found that the products of photo-oxidation of dibenzanthracene are

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* This paper is based on work performed under Contract W-7405-Eng-48 with the Atomic Energy Commission in connection with the Radiation Laboratory, University of California, Berkeley, California. Preliminary reports of this work were presented at the meeting of the American Association for Cancer Research, Inc., in Chicago, May, 1947, at the Fourth International Cancer Congress, St. Louis, Sept., 1947, and at the 50th anniversary meeting of the Columbus Section of the American Chemical Society, October, 1947.

Received for publication, February 26, 1948.

different from the water-soluble materials produced by metabolism in the mouse.

EXPERIMENTAL METHODS

In order to compare the type and extent of metabolic degradation of dibenzanthracene following various modes of administration to mice, these samples were collected: feces, urine, and bile from animals given the carcinogen intravenously as an aqueous colloid and intraperitoneally in tricapylin; feces and urine after stomach-tube administration in tricapylin; feces and injection sites following subcutaneous injection in tricapylin; and tumors induced by the labeled dibenzanthracene. The bile samples were collected throughout one day; and the total urine and feces, three days after administration. These specimens were then subjected to the extraction procedure shown in Fig. 1.

The feces were dried at 70° in vacuum, ground to a fine powder, and the radioactivity determined after combustion of an aliquot as described previously.¹⁰ An aliquot of the urines was plated directly, a little dilute sodium hydroxide added to the remainder, and the water removed as the azeotrope during the prolonged benzene extraction. Biles were evaporated to dryness after an aliquot was plated directly and a trace of alkali added. Injection sites and tumors were homogenized, and the activity determined by combustion of a sample. A little alkali was added, and the water removed as the azeotrope during the benzene extraction.

The liquid-solid extractions were carried out in small flasks fitted with reflux condensers; the liquid-liquid extractions were performed entirely in centrifuge tubes, the upper layer being removed with a pipette. The radioactivity of both fractions was determined in all cases, so that a constant check was maintained on total quantities, and losses might be spotted immediately. Moreover, this procedure furnished partition coefficients for each step, information very valuable for attempts at complete chemical identifications.

The radioactivities of solid samples were determined after combustion, as described previously.¹⁰ Liquid samples were plated di-

rectly* and counted with a thin-window Geiger-Müller counter. The empty plate was mounted on a rotating turntable with a blast of hot air from a hair dryer directed upon it. An aliquot of the solution to be measured was slowly expelled, by means of a syringe, from a micropipette onto the rotating plate in such a way that the solvent evaporated immediately and the residue was spread evenly on the plate. Because the weight of sample on the plate seldom exceeds a few tenths of a milligram, the self-absorption of the β -particle may be neglected. The accuracy of this method is not so great as that obtained when barium carbonate is mounted, but the advantages of speed, convenience, and the fact that the sample is not destroyed make this technique ideal for the type of work described here. The total experimental error on each sample did not exceed 10 per cent—substantiated by the excellent recoveries in the extraction experiments. This method also makes it possible to gain considerable information about the organic chemistry of labeled compounds on the microgram scale. It is, of course, unsuitable for the assay of volatile compounds.

A summary of the results obtained in the extraction experiments is shown in Table 1. These are expressed as counts per minute and as percentage of the radioactivity in the original sample. The total counts recovered are also expressed as the number of milligrams of dibenzanthracene to which the radioactivity would be equivalent. It is quite evident from casual inspection of these data that dibenzanthracene is very extensively metabolized by the mouse to other substances differing widely from the original carcinogen in chemical characteristics. However, in order to gain more detailed information as to the chemistry of the various fractions, each was subjected to further examination.

Dibenzanthracene. The dibenzanthracene was determined by means of carrier technique. A known amount of nonlabeled dibenzanthracene was added during the fractionation and was crystallized from the benzene

* This technique was devised by Dr. A. A. Benson of these laboratories.

TABLE I
SUMMARY OF RESULTS OBTAINED IN EXTRACTION EXPERIMENTS

	<i>Total cts. re- covered (mg. of DBA) (%)</i>	<i>Fractions</i>									
		A	B	C	D	E	F	G	H	I	% Recovery
Intravenous: feces	12,900 (0.193)	730 117 5.6%	1870 14%	2190 17%	I 127 5.8%	I 1900 15%	I 0	2050 16%	4770 37%	760 5.9%	56% (spill in 1st step)
Intravenous: urine	1180 (0.018)	47 0.77 4.0%	170 15%	610 52%	I 0	I 354 30%	I 113 19%	32 2.7%	300 26%	0	85%
Intravenous: bile	2600 (0.039)	600 9.07 23%	20 0.7%	1900 73%	I 60 2%	I 1800 69%	I 0	80 3.0%	0	0	90%
Intraperitoneal: feces	11,000 (0.164)	130 1.97 1.2%	460 4.2%	80 0.7%	87 0.7%	680 37%	156 8.5%	18 1.0%	3000 27%	1400 13%	87%
Intraperitoneal: urine	1780 (0.027)	35 0.537 2.0%	490 24%	870 48%	I 87 4.8%	I 680 37%	I 156 8.5%	18 1.0%	450 25%	0	103%
Intraperitoneal: bile	880 (0.013)	50 0.757 7%	140 20%	460 64%	I 110 16%	I 410 58%	I 36 5%	0	30 4%	0	81%
Stomach tube: feces	8620 (0.130)	3900 587 45%	510 6%	810 9%	I 180 2.1%	I 450 5.2%	I 60 0.7%	90 1.0%	2700 31%	460 5.3%	86%
Stomach tube: urine	3360 (0.050)	150 2.27 4.5%	620 18%	1800 54%	I 70 2%	I 670 20%	I 840 25%	100 3%	690 20%	0	90%

TABLE I—Continued

Total cls. re- covered (mg. of DBA)	Fractions										
	DBA (%)	A	B	C	D	E	F	G	H	I	% Recovery
Subcutaneous: feces	2820 (0.047)	305 4.57 11%	400 14%	200 7%	2 110 3.9%	2 110 3.9%	2 285 10%	345 12%	1100 39%	465 17%	93%
Subcutaneous injection site, 1 wk.	45,300 (0.675)	44,100 6607 97%	730 1.5%								100%
Subcutaneous injection site, 3 mos.	4160 (0.062)	4020 607 96.5%	135 3.5%								100%
Tumor: 6 mos., tricaprylin, hyperkeratosis of skin with early spindle-cell sarcoma	460 (0.0069)	460 6.97 100%									100%
Tumor: 10 mos., mouse fat, spindle-cell sarcoma	577 (0.0086)	310 4.67 54%	90 13%	127 22%				0	50 8.7%	0	84%
Tumor: 6 mos., mouse fat, spindle-cell sarcoma	1050 (0.016)	160 2.47 15%	0	240 23%	1 72 0.6%	1 216 21%	1 0	330 32%	270 25%	0	79%
Tumor: 6 mos., tricaprylin, spindle-cell sarcoma	4030 (0.060)	3700 557 92%	0	29 0.7%				113 2.8%	190 4.7%	0	98%
Tumor: 8 mos., tricaprylin, spindle-cell sarcoma with marked hyalinization	4200 (0.063)	4130 627 99%	0								99%
Photo-oxidation, 1 hr. in benzene solution	40,500 (0.605)	29,700 4507 73%						(NaHCO ₃) 7500 18.5%	2900 7.2%	0	100%

solution. It was purified by two recrystallizations, one from acetic acid, and the other from benzene. The dibenzanthracene was combusted and its radioactivity determined. Under these conditions this radioactivity could only originate from the labeled carcinogen, so that this furnishes an extremely accurate and sensitive method for the quantitative determination of nonmetabolized, labeled dibenzanthracene on the microgram scale.

The benzene solution from which the dibenzanthracene was crystallized contained no other labeled compounds, because activity measurements on this solution always corresponded closely to the activity of the total dibenzanthracene.

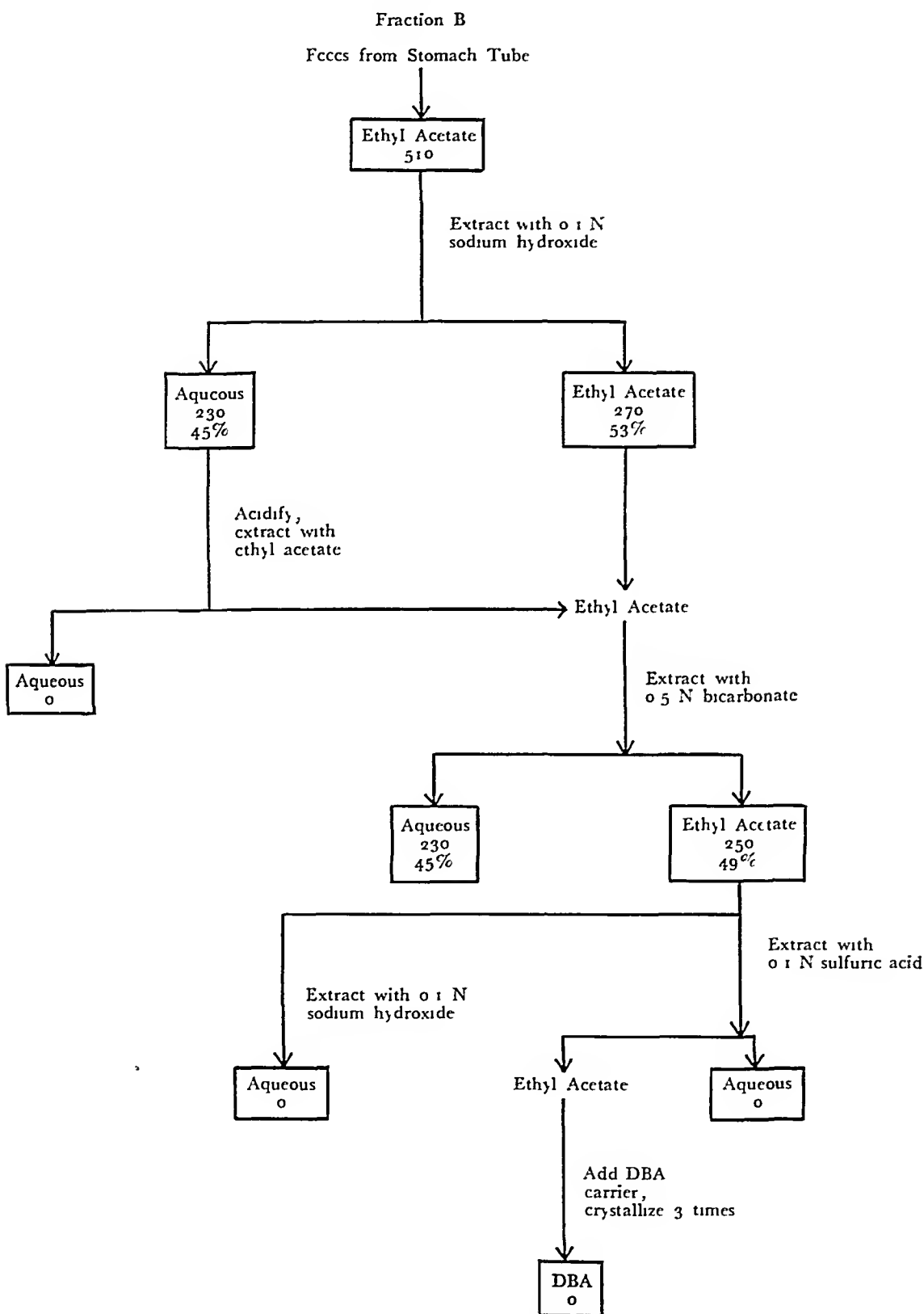
Fraction B. This fraction contained organic material that was probably unconjugated, since it was obtained by very mild treatment. This was also the fraction that would contain dihydroxydibenzanthracene if not conjugated. Unfortunately, none of this compound was available for use as carrier. Figure 2 represents an attempt to gain further information about its chemical components. It shows that there was acidic material present that was extracted by bicarbonate. However, further extraction of the organic phase with alkali did not remove more activity, indicating that no phenolic compounds were present in this mixture. Furthermore, a very considerable amount of activity was present in this fraction that was not extracted with acid or alkali. This neutral material was not dibenzanthracene, for no radioactivity was found in carrier dibenzanthracene added to the solution. Evidently, it was some neutral metabolite that had not been taken up in the original benzene extraction.

In order to detect dihydroxydibenzanthracene with more certainty, the experiment shown in Fig. 3 was carried out. Fraction B was acetylated under the conditions described by Cason and Fieser, and the mixture was made alkaline and extracted with ethyl acetate. The activity remaining in the aqueous phase was derived from acidic material. The ethyl-acetate layer was hydrolyzed with alkali and re-extracted with ethyl acetate. There was radioactivity in the alkali this time,

which was taken up in the organic solvent after acidification. This represented phenolic material and was probably dihydroxydibenzanthracene, although there was no further evidence on this point. This fraction only accounted for 15 per cent of the radioactivity in fraction B, or 2.7 per cent of the activity in the entire feces sample. Again a considerable amount of neutral material was found that was not affected by drastic acid and alkaline hydrolysis.

Fraction C. This fraction appeared to consist of some extremely water-soluble organic substances together with some less soluble material that was conjugated with water-solubilizing groups. Fraction C was split by hydrolysis into fractions D, E, and F. Procedure 1 was an alkaline hydrolysis, procedure 2, an acid hydrolysis, as indicated in Table 1 and Fig. 1. Fraction D contained the substances that were conjugated with solubilizing groups, and was acidic in nature, for most of the activity was extracted from the ethyl acetate by alkaline solution. The radioactive components of fraction E were in truly water-soluble form, even after rather drastic hydrolytic treatment. They were not extracted by ethyl acetate from the aqueous phase at acidic or basic pH's or at neutrality. Fraction F was a solid that appeared after hydrolysis and carried considerable activity. The solid must have been a component of the urine or feces, since several milligrams of material were invariably obtained, whereas the radioactivity it carried generally corresponded to only a few micrograms of compound. The solid was usually soluble in alkali, as was the radioactive component, but this varied from sample to sample, and little progress has yet been made in the separation of the radioactive compounds from this solid carrier. Thus, the chemical nature of this fraction is not clearly known, although it appears to be acidic, and yet is not extracted by organic solvents.

Fraction G. After the removal of fractions B and C, the solid residue from the original sample, when boiled with water, gave fraction G. This, like E, consisted of truly water-soluble material together with some substance



Fraction B

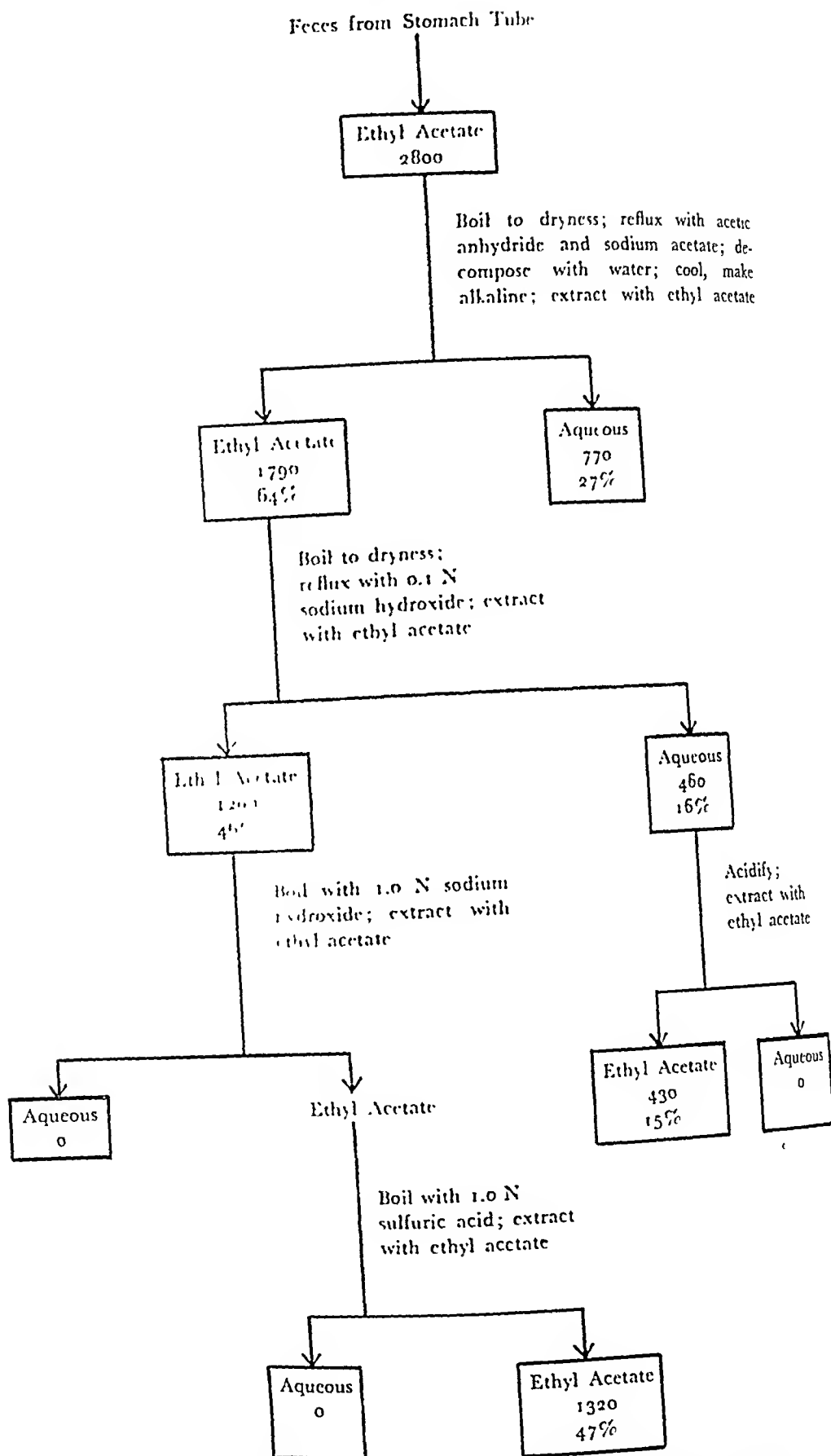


FIG. 3. Extraction of fraction B to detect dihydroxydibenzanthracene.

that was rendered soluble by conjugation. Further processing of this fraction is shown in Fig. 4; similar results were obtained from several other samples. Again, troublesome solids were encountered that have not been further characterized. These results indicate that the ethyl-acetate fraction is very similar to the acidic material of fraction B. If the organic compound containing the labeled carbon is the same, however, it was present in conjugated form in fraction G, since it had been made water-soluble. It also appears that the water-soluble fraction after hydrolysis is the same as fraction E. These points of similarity cannot be completely confirmed until the final identification of the compounds in these fractions has been accomplished.

Fraction H. Boiling the solid residue from fraction G with alkali yielded fraction H. It contained acidic and water-soluble substances that were released by alkaline hydrolysis and were probably conjugated with proteins and other solid material. Further processing of this sample is shown in Fig. 5; the results correspond closely with those obtained by similar treatment of other samples. Again, ethyl acetate did not extract any radioactivity from the water-soluble fraction whether the solution was basic, acidic, or neutral. The distribution of activity of the alkaline extract of the ethyl-acetate solution suggests that this fraction might contain acidic material very similar to that found in other ethyl-acetate fractions, such as B and D. The precipitate, formed on acidification of the original solution, was partially dissolved in alkali; on reacidification, an appreciable amount of radioactivity was extracted by ethyl acetate.

Fraction I. In some samples radioactivity was still present in the residue from the alkaline extraction, fraction H. When this residue was refluxed with dilute sulfuric acid, no activity appeared in the aqueous phase. However, when the residue was then extracted with alkali, radioactivity appeared in the aqueous solution. This activity represents acidic compounds that are possibly conjugated with protein or other material in such a way that they are hydrolyzed by acid and not by base.

Figure 6. At the kind suggestion of Dr. James Cason, who called our attention to the fact that dihydroxydibenzanthracene is very unstable in acidic solution, the experiment shown in Fig. 6 was carried out to determine whether some of the "metabolites" encountered in the previously described work might have arisen from the phenolic compound as an artifact during the isolation procedure.

The feces sample was acetylated before further processing in order to protect any dihydroxydibenzanthracene that might be present, then treated with ethyl acetate to extract fraction 1. This was then hydrolyzed with alkali and re-extracted with ethyl acetate. Carrier dibenzanthracene was added to this fraction; after purification, it was found that 6.5 per cent of the activity was due to the unchanged carcinogen. This represents 1.6% of compound. Fraction 2 was acidified and extracted with ethyl acetate; fraction 3 contained phenolic material, probably dihydroxydibenzanthracene.

The solid precipitate, fraction 4, was refluxed with alkali, and the residual solid, fraction 5, was not further investigated. The aqueous solution was acidified, extracted with ethyl acetate, and re-acetylated. Further processing resulted in various fractions of which number 8 is phenolic in nature. Thus, fractions 3 and 8, which account for almost 14 per cent of the radioactivity in the entire specimen, are phenolic in nature; fractions 7, 9, and 10 contain 31 per cent of the activity and are water-soluble. Fraction 5 was not further investigated, but in the light of other experiments, it very likely consists of water-soluble substances in conjugated form. This appreciable amount of phenolic material is greater than has been previously observed in other investigations and in our other experiments, and indicates that some of the degradation products may have arisen from a phenolic compound (probably dihydroxydibenzanthracene) during the isolation procedure.

METABOLIC DEGRADATION FOLLOWING DIFFERENT MODES OF ADMINISTRATION

Intravenous Administration. It is apparent from Table 1 that dibenzanthracene admin-

Fraction G

Feces from Intravenous Injection

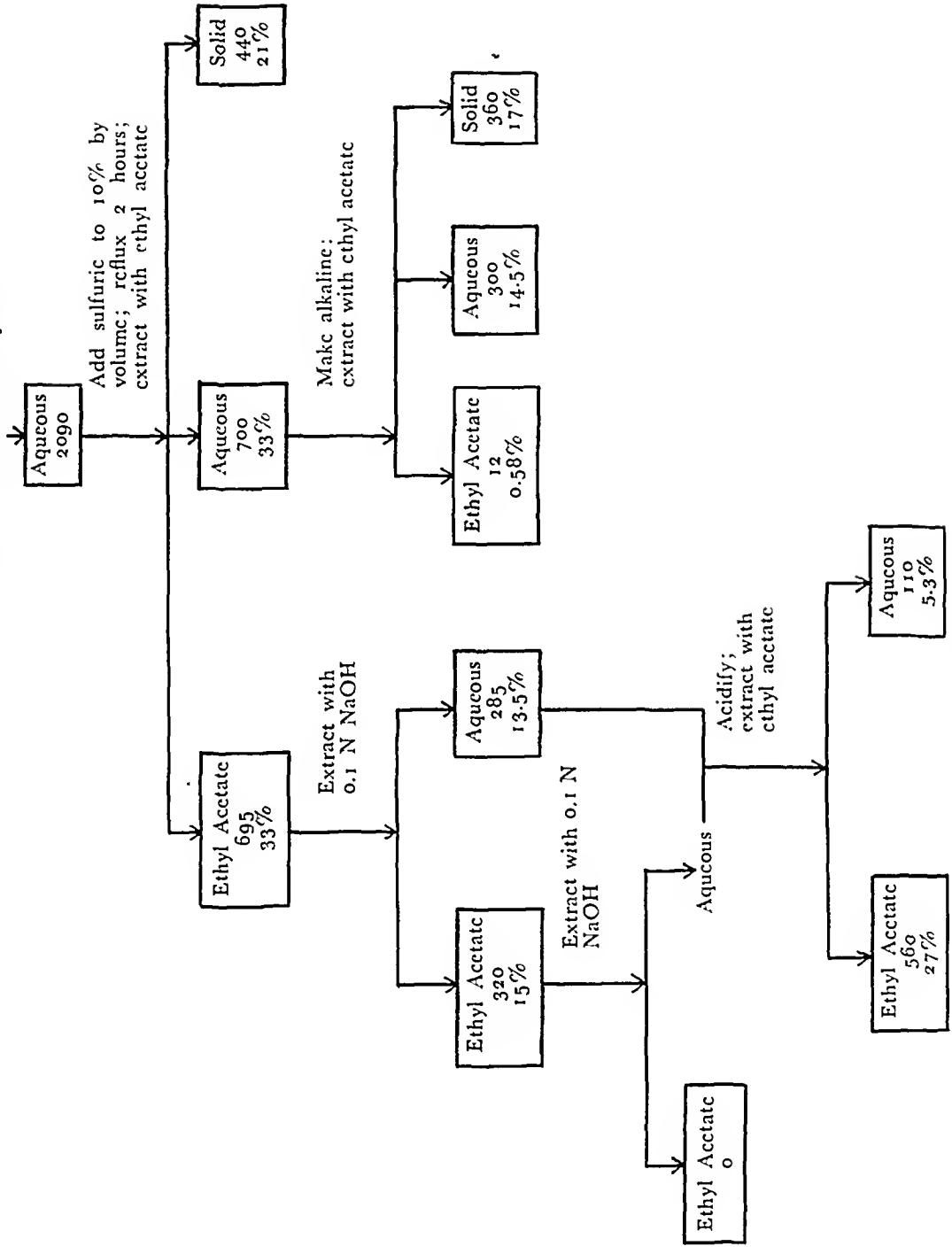


FIG. 4. Extraction of fraction G.

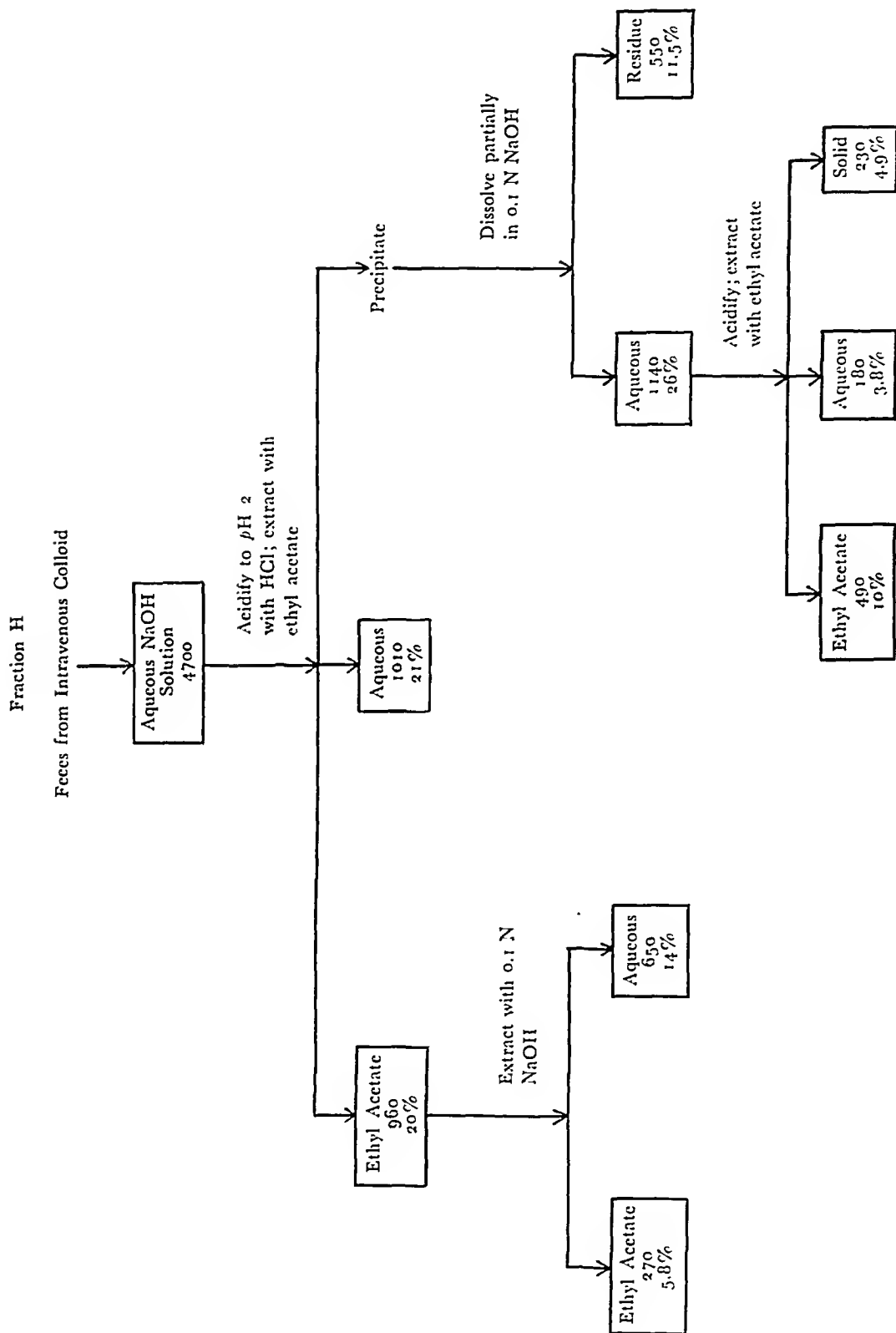


Fig. 5. Extraction of fraction H.

istered by intravenous injection of the aqueous colloid was very extensively degraded, since only 5.6 per cent and 4.0 per cent of the radioactivity in the feces and urine respectively was due to dibenzanthracene itself. These activities correspond to 11 and 0.7% of the carcinogen. It is clear from the data for the bile, that the liver is one of the sites of degradation, because there is only 26 per cent of dibenzanthracene radioactivity in the sample and it has already been shown¹⁰ that there is immediate uptake of the radioactive compounds by the liver which then empties them into the bile. Since it has also been demonstrated that the only source of radioactivity in the intestinal contents is derived from the bile, it is evident that further degradation takes place in the intestinal tract, because the quantity of nonmetabolized carcinogen in the feces is considerably smaller than in the bile. It might be surprising that such a large and insoluble molecule could be eliminated through the kidneys and appear in the urine, but similar observations have been made by spectroscopic methods.¹¹ It is possible, however, that this may have arisen because of contamination of the urine by the feces, since it was impossible to prevent these excreta from coming into contact with each other under the conditions of our experiments. The B fraction contains considerably more activity in the urine and feces than does the bile. The absence of an H fraction in the bile probably indicates only that the metabolite does not conjugate with the components of the bile.

Stomach-Tube Administration. There is a considerably larger amount of unchanged dibenzanthracene in the feces (45 per cent) by this route than by the others, but only 4.5 per cent of the radioactivity in the urine sample can be accounted for as dibenzanthracene. This probably indicates that the intestinal tract is not so efficient as the liver in metabolizing the compound. The majority of the water-soluble material in the feces is bound in some way (fraction H), whereas in the urine most of the activity appears in fraction C and is in a less conjugated state. However, the degradation in these cases must take place exclusively in the gastrointestinal tract.

Intraperitoneal Administration. There is very extensive metabolism of dibenzanthracene administered intraperitoneally, but the exact mechanism of absorption and elimination by this route is by no means clear as yet. The B fractions of the urine and bile are unusually high, and there is a very appreciable I fraction in the feces. The very small amount of dibenzanthracene eliminated in the feces (1.2 per cent) is in accord with the observations of Berenblum and Kendal, who were unable to detect any dibenzanthracene fluorescence in feces collected from mice that had been given the compound intraperitoneally.

Subcutaneous Administration. Fractionations performed on the sites of subcutaneous injection after one week and three months show that there is no appreciable degradation of the dibenzanthracene. It has already been demonstrated that most of the radioactivity lost from the site appears in the feces, and fractionation of the feces indicates a very substantial metabolism of the compound (only 11 per cent of the radioactivity is due to the carcinogen). Thus it appears that the dibenzanthracene leaves the site of subcutaneous injection intact, but is then degraded during the process of elimination from the body.

Tumors Induced by the Labeled Carcinogen. Several tumors, induced by the radioactive dibenzanthracene, have been fractionated to determine the extent of degradation. (For the per cent of injected radioactive material in these tumors see Table 7 in the accompanying paper.¹⁰) There appears to be a considerable individual variation among these. In three of the tumors more than 90 per cent of the radioactivity was due to unchanged dibenzanthracene. However, it is striking that in two of the tumors, the carcinogen had been extensively degraded (only 15 per cent and 54 per cent of the activity was due to dibenzanthracene). Since there is no evidence that under normal conditions any degradation occurs at the site of subcutaneous injection, these results suggest that neoplastic tissue is capable of degrading the carcinogen, whereas normal tissue cannot. Obviously,

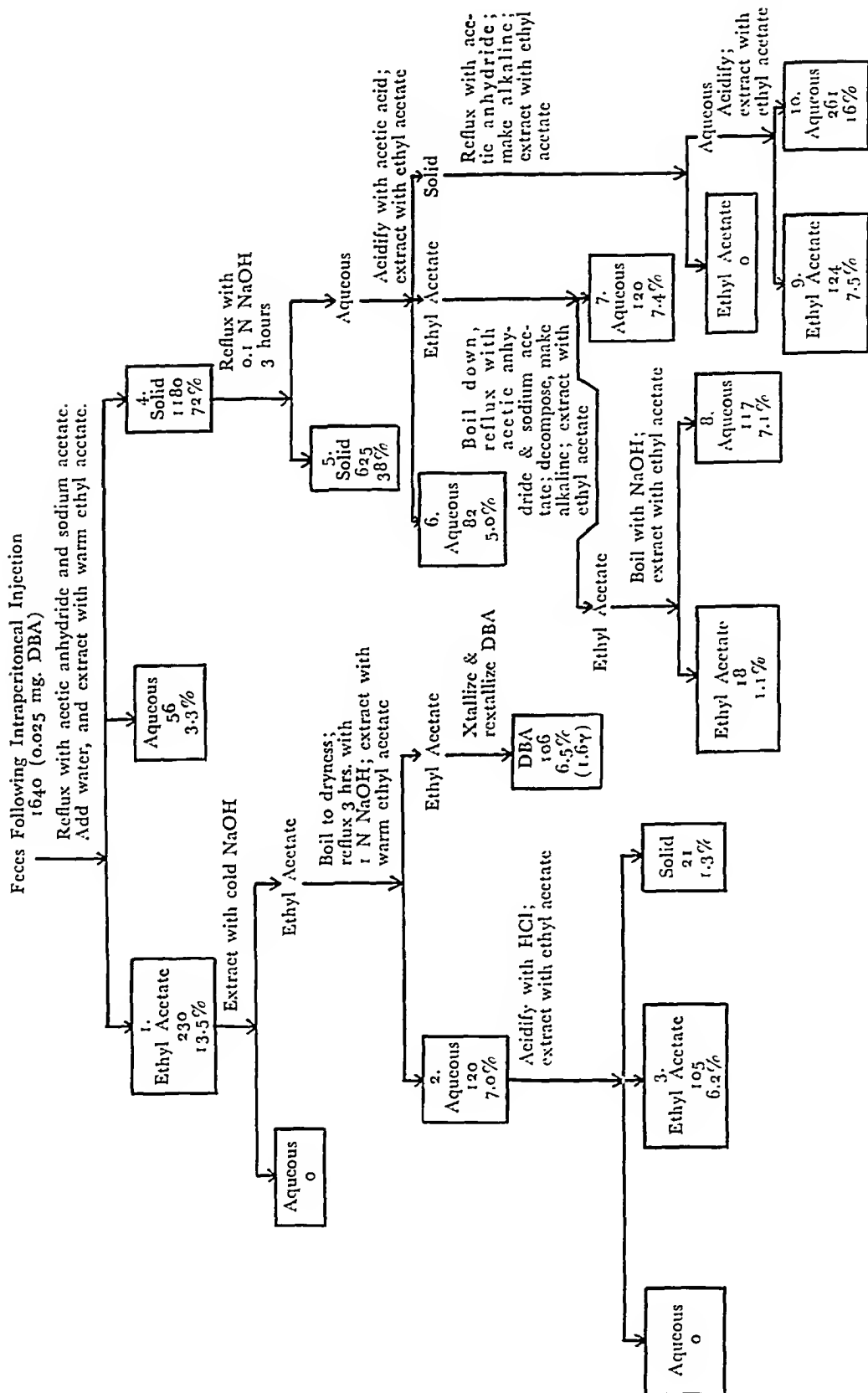


FIG. 6. Extraction to determine whether some "metabolites" encountered previously might have arisen from the phenolic compound as an artifact.

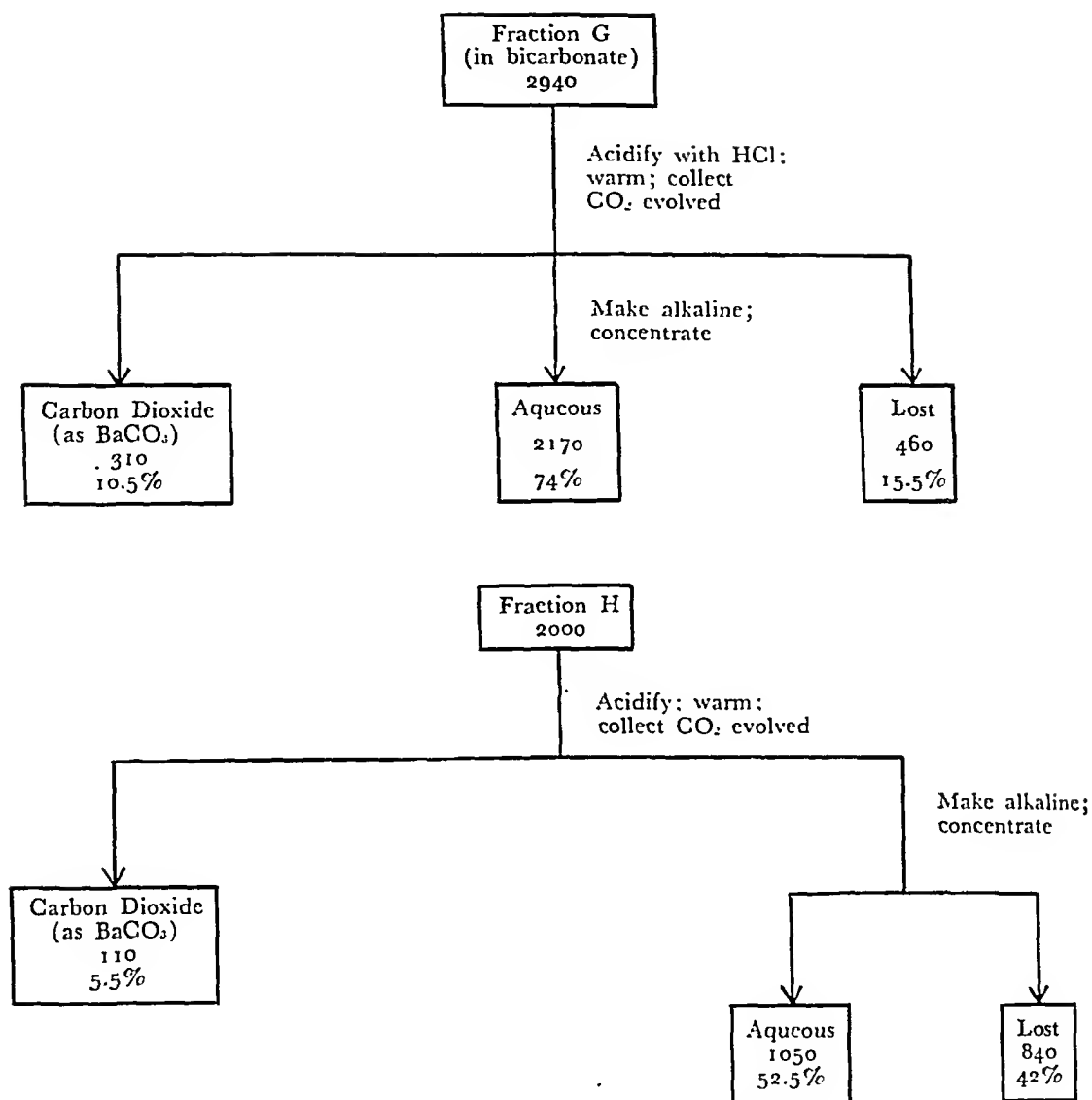


FIG. 7. Photo-oxidation of dibenzanthracene.

more experiments must be done before this point can be settled.

Photo-oxidation of Dibenzanthracene. Labeled dibenzanthracene was photo-oxidized in benzene solution by exposure for one hour to a mercury-vapor arc, according to the procedure of Allsopp and Szigeti. The resulting mixture was processed in almost the usual way, except that fractions B and C were not obtained, and fraction G was a bicarbonate extraction. The products were unstable, for when fractions G and H were acidified and warmed, as shown in Fig. 7, radioactive carbon dioxide was eliminated. There was also an appreciable loss of over-all activity when alkaline solutions were concentrated at atmospheric pressure, suggesting perhaps that volatile neutral substances were formed during the reaction. These observations suffice to prove that the water-soluble metabolites are not closely related to the photo-oxidation products, because the former never exhibit this instability.

DISCUSSION OF RESULTS

Evidence has been presented proving that dibenzanthracene is metabolized by the mouse into at least four substances, and some

speculations as to the sites of this degradation have been advanced. It is possible that a small amount of these compounds is produced as an artifact from dihydroxydibenzanthracene during the isolation procedure.

The fact that unchanged dibenzanthracene is found in tumors six to eight months after their induction is interesting; it had previously been demonstrated spectrophotometrically by Lorenz and Shear. This observation, it must be emphasized, does not throw any light on the problem of whether the original hydrocarbon is the true carcinogen, or whether some metabolite is. In view of the increasing body of evidence^{2,3,9,14} that only very minute quantities of carcinogenic hydrocarbons are required to initiate the irreversible process that leads to the tumor, the fact that appreciable amounts of dibenzanthracene are found in the tumor is of little more than academic interest. Indeed, it seems likely that the metabolic degradation described here is merely a detoxication process quite unrelated to the initiation of cancer.

This work is being continued with the aim of elucidating the structures of these metabolites, and the various fractions described are being tested both for carcinogenic and tumor-regressive properties.

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THE ROENTGENOGRAPHIC APPEARANCE OF RENAL CANCER METASTASIS IN BONE

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DURING the course of our routine work it occurred to us that renal cancer metastatic to bone might occasionally present certain unique characteristics in the roentgenogram. To test the value of this impression we have studied the material available at Memorial Hospital from the standpoint of roentgen-ray diagnosis.

This consists of thirty-six proved cases of renal cancer metastases in bone that have adequate roentgenographic coverage. Each case had at least one pathological report indicating renal cancer origin, based on tissue from the primary tumor, from the metastasis, or in certain instances from both. The pathological diagnosis might have come from the surgical specimen or biopsy, aspiration biopsy, or post-mortem specimen. If biopsy of a metastasis were reported as cancer, indicative of renal origin, and if, in addition, pyelographic evidence of renal tumor were conclusive, the case was accepted. Similarly, if a renal cancer were removed and metastases were subsequently revealed in the bones, the case was included. In no instance does diagnosis rest on roentgenographic evidence alone.

Early studies on metastases to bone from renal cancer were made by Seudder and Gibson and Bloodgood. The latter, in commenting on radiographic appearance, stated that the lesion was always destructive without any element of production, and that there were no roentgenographic findings that differentiated "hypernephroma" from any other form of skeletal carcinomatous metastases.

More recent reports were made by Copeland, Fort, Gillies, Turner and Jaffe, Herger and Sauer, and Abeshouse. When the radiographic appearance was commented upon,

renal cancer metastases in bone were held to be generally osteolytic and to show no specific features. Recently Fried collected eighty-seven cases of renal cancer from the files of Montefiore Hospital: 45 per cent, or thirty-nine cases, had metastasized to bone. In 43 per cent of these thirty-nine, the involvement was solitary. Fried stated that the osseous lesions were always destructive, rarely produced new bone. He was chiefly interested in roentgen-ray treatment and reported little if any local symptomatic improvement, and occasionally growth continued in spite of radiation.

CLINICAL FEATURES

Twenty-three of our thirty-six cases were in men, thirteen in women. The age range of the patients was from 27 to 70 years. In twenty-eight, the first symptom that was responsible for the initial visit to the physician was the disease in bone. Pain was the outstanding complaint in thirty-two cases. In twenty-one, localized swelling was revealed. Four patients had pulsating tumors.

Ten patients had had a renal cancer removed previously. The time interval between the nephrectomy and the appearance of the metastasis varied as follows: one, one month; four, one year; one, two and one-half years; one, three years; two, six years; one, ten years.

The Pathological Laboratories of Memorial Hospital made the following diagnoses: adenocarcinoma, renal type, twenty-five cases; renal carcinoma, six; "hypernephroma," three; embryonal carcinoma, two. No correlation between the cell type and the roentgenographic appearance of the metastases was evident.

A primary bone tumor was diagnosed clinically in thirteen patients, osteogenic sarcoma being the most frequently suspected. Other clinical diagnoses were endothelioma.

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Received for publication, February 20, 1948.

angioma, cancer of the lung, parotid tumor. Brodie's abscess, myeloma, and "cyst." Fourteen cases were diagnosed as metastases. Some patients came to the hospital with the correct diagnosis previously established. In a number no clinical diagnosis was offered.

Eighteen cases were diagnosed roentgenologically as metastatic. An additional four were described simply as "bone destruction" while some were called "malignant tumor." There were four cases, however, in which the roentgenographic diagnosis was osteogenic sarcoma. There were instances in which diagnoses of myeloma, hemangioma, and even giant-cell tumor and bone cyst were offered. In no instance was the diagnosis of renal cancer metastasis made on the basis of the roentgenographic appearance alone.

The number of incorrect diagnoses, both clinical and roentgenographic, and even the

occasional indeterminate pathological report, emphasizes a difficulty that, in our experience, is not usually encountered in metastases secondary to primary cancer in breast, lung, prostate, or less common sources (Fig. 1). In fact, amputation has been done on a mistaken diagnosis of primary bone tumor. This difficulty is probably due not only to our failure, in the past, to appreciate the varied appearance of renal cancer in bone, but also to the tendency of this form of primary growth to remain silent, the relatively slow rate of growth of some renal cancers, and the rather high percentage of "solitary" metastases. It is hoped that the present study will improve our roentgenographic diagnoses in the future.

ROENTGENOGRAPHIC DIAGNOSIS

In attempting to determine the roentgeno-

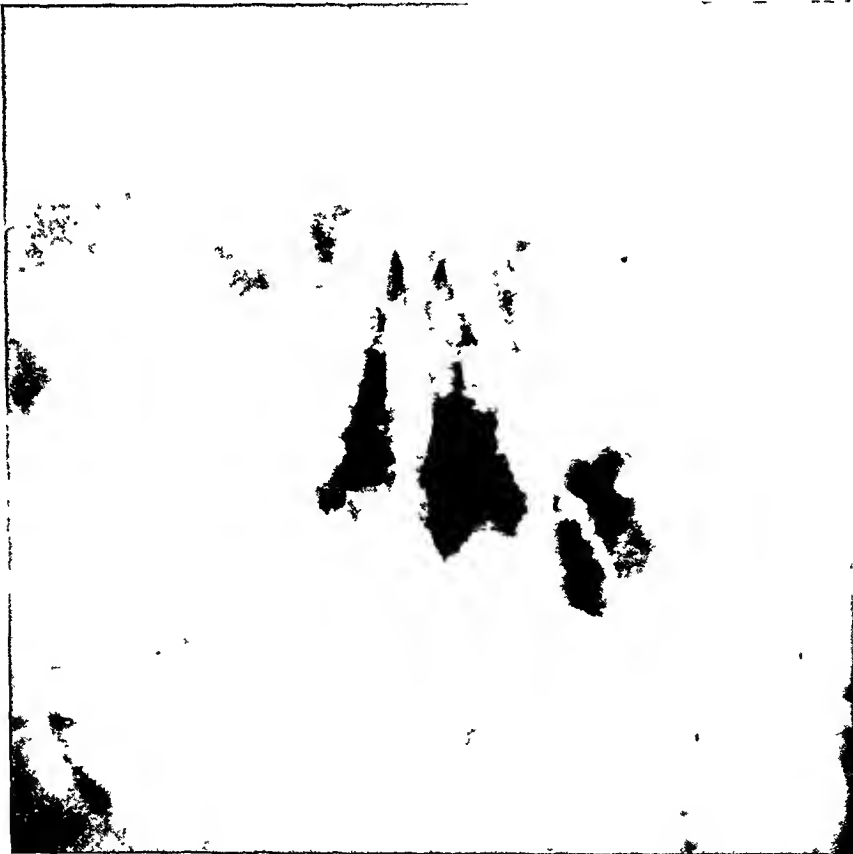


FIG. 1. *Cancer metastasis in an unusual site diagnosed clinically and radiographically as carcinoma of the antrum. A qualified pathological report of angiosarcoma of bone on biopsy was given. Autopsy proof of renal primary tumor followed.*

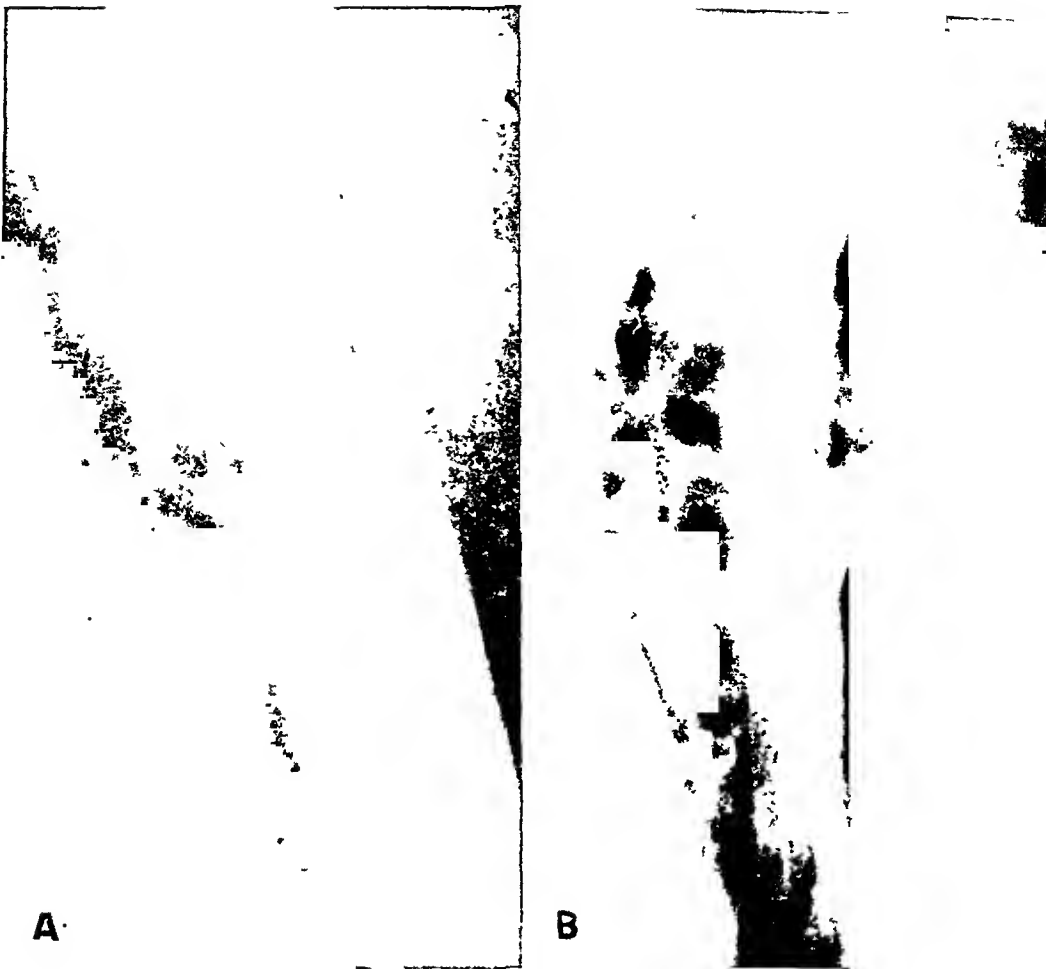


FIG. 2. A, *Lytic type cancer metastasis in the shaft of the humerus with pathological fracture.* B, *After roentgen-ray treatment the fracture healed. The metastasis now resembles the septate form. This is an instance of exceptional response to roentgen-ray treatment.*

graphic appearance of renal cancer metastatic to bone, we intend to follow the more or less standard plan that we pursue in making a roentgenographic diagnosis in any case of bone tumor. This system recognizes, as the logical and productive approach, the need to analyze each of the basic features that may be encountered.

The following information derives from an examination of the earliest roentgenogram available in each instance. Later on, subsequent negatives were studied to note the effects of growth and of treatment as the case might be.

Based upon roentgenographic evidence, twenty-one of the thirty-six cases were "solitary," i.e., only a single metastasis was revealed in the roentgenograms. In the fifteen

instances where two or more tumors were seen, the largest or most significant tumor was described, because it had been found that all the metastases in any one case were fundamentally alike.

Location in Skeleton. The twenty-one instances of solitary metastases were distributed as follows:

humerus	4	maxilla	1
pelvis	4	skull	1
femur	3	rib	1
spine	2	scapula	1
mandible	2	tibia	1
		fibula	1

In the fifteen patients showing two or more areas of metastases an equally diffuse distribution in the skeleton was encountered. It is



FIG. 3. Patchy type of cancer metastasis showing an unusual degree of periosteal reaction for kidney cancer metastasis.

evident that there is no significant site of predilection for renal tumor metastases to bone in this series.

Location in Bone. By this we refer to the part of bone involved, i.e., epiphysis, metaphysis, or diaphysis. Application of this feature is limited to the tubular bones. There were fifteen cases in which the lesion was in a long bone. Of these, three were in mid-shaft, ten toward the ends, and two at the ends, i.e., in the former epiphyscal areas.

Site of Origin. It is usually possible to determine whether a tumor arises from the cortical or the medullary portion of a bone. In thirty-four of the thirty-six cases, the medulla was thought to be the site of origin. Cortical and medullary origin could not be

differentiated in two tumors arising in the maxilla. There was no instance of subperiosteal cancer metastasis noted in this material.

Symmetry in Bone. This term refers to the position of the tumor relative to the long axis of the bone in both sagittal and lateral projections and applies specifically to tumors in the tubular bones. There were nineteen in which symmetry could not be determined. Of the remainder, fifteen were symmetrically



FIG. 4. Septate type of cancer metastasis in the distal portion of the shaft of the femur.

positioned and two were not. In the tubular bones, therefore, symmetry is to be expected in renal tumor metastases.

Direction of Growth. Many times it is possible to postulate the growth direction of tumors occurring in bones. Some tend to travel and extend within the bone itself, while others may break out of the bone relatively early and expand in the periosteous structures. There were twenty tumors in which no clear distinction between these two different courses of growth could be discerned. In twelve, growth seemed to occur principally within the bone, and in four there was an early or pronounced tendency to grow outward, beyond the bone.

General Configuration. The over-all shape of a bone tumor may be one of its important roentgenographic characteristics. In determining shape, both the osseous and the peri-

osseous part of the lesion must be considered and both sagittal and lateral views are necessary to reconstruct three dimensional aspects. Only a general statement pertaining to shape is indicated; terms such as spherical, oval, and fusiform are sufficiently informative. There were three cases with spherical metastases, three with fusiform, and twenty-seven with oval metastases. There were three instances in which the general configuration could not be determined with assurance. It seems that an oval shape is the one to be expected in renal cancer metastases in bone.

Destruction and Production in Medullary Bone. In judging the degree of destruction and production, the density of the normal neighboring bone was used as the basis of comparison. Calcification and the formation of normal or abnormal bone were considered productive changes. Destruction of medul-



FIG. 5. An unusually large metastasis of the septate type in the ilium. This is to be differentiated from the "solitary" form of myeloma.



FIG. 6. *Septate form in the distal portion of the shaft of the femur.*

lary bone was present to some degree in each of the thirty-six cases. In seventeen, it was unaccompanied by any productive change; in sixteen, destruction predominated over varying degrees of productive change, while in three destruction and production were considered to be about equal in degree. In no tumor did production predominate. Destruction of bone is thus seen to be a constant finding in renal cancer metastases. In thirty-three of the thirty-six cases it was present to a greater degree than productive change. In no case was production the outstanding feature.

Pattern. Eighteen tumors had no internal pattern whatsoever (Fig. 2 A). In an additional nine there were either a few scattered indefinite calcific flecks or a few sketchy incomplete septa within the area of destruction. These twenty-seven cases were designated the lytic-pattern tumors.

In three cases, the pattern of the tumor

showed fine patchy areas of destruction around which there seemed to be nearly normal-appearing bone. While these were predominantly destructive lesions, the total amount of destruction was relatively small compared to the tumor area (Fig. 3). This pattern was called the patchy type.

There were six tumors in which the structure was unusual. These were characterized by large, well-formed, coarse, heavy septa running through the area of destruction. These six cases were designated as the septate type (Figs. 4, 5, and 6).

Boundary. The boundary of a tumor includes all portions, both osseous and periosteous. The border in these tumors varied from indistinct to clear-cut. Except for the fact that the periphery of these lesions was generally more apparent than is the case for metastases in general, no further significance could be attached to this feature.

Cortex. Destruction of the cortex was found in varying degrees in thirty-five of the cases. In one there was evidence indicating slight cortical expansion. The destruction varied from a tiny area of erosion to large areas of cortical bone loss. Cortical destruction appears to be another rather constant feature for this type of cancer metastasis.

Periosteum. In thirty-one instances in this series there was no periosteal reaction evident on the initial roentgenograms. In several of these thirty-one, however, periosteal reaction would not be expected to show, for instance, in those lesions in the vertebrae or in the maxilla. A reaction of the periosteum did occur five times, in three of which the change was graded as moderate and in two as minimal. In these five cases there was a perpendicular type of reaction twice and a parallel type four times, the two forms being recognized simultaneously in one instance.

Periosteous Mass. A mass extrinsic to the bone was formed in twenty-nine cases. In seven the mass was small, in fifteen it was moderate in size, and in seven it was described as large. In general, the size of the soft-tissue mass was related to the size of the osseous part of the tumor, so that in those called "moderate periosteous mass" the area

of bone involvement and the size of the soft-tissue mass were approximately equal.

Joint Changes. Occasionally tumors occurring at or near a joint can cause changes in the joint that may be of value in formulating a roentgenographic diagnosis. "Synovitis" and growth into or even across a joint are examples of such findings. There was no evidence of "synovitis" in this group. None of the large body joints showed any significant effect.

Pathological Fracture. There were fourteen pathological fractures in this series. In several tumors the bone was so destroyed that any semblance of continuity had vanished, but the general alignment did not seem essentially disturbed. The fractures were found in the spine and in the tubular bones. In one case several fractures were present. There was a single instance in which a patho-

logical fracture had healed well under roentgen-ray treatment (Fig. 2 B).

Rate of Growth. In eleven cases it was possible to make some estimate of the rate of growth. All had received varying amounts of roentgen-ray treatment, so that there is no case in which growth uncomplicated by any outside factor can be judged.

Observation periods varied from several months to two years in one instance, the average time being around eight months. There was only one tumor in this group that did not seem to have grown during the observation period, in spite of the fact that all had received roentgen-ray treatment. One seemed to enlarge by about 10 per cent in two years, and there were two others that appeared to grow at about this rate. One of the most rapidly enlarging lesions became five times larger in an eight-month period.



FIG. 7. Predominantly lytic type of metastasis but with sufficient septa formation to warrant suggesting renal origin.

The average rate would seem to be a 50 per cent growth in five to seven months in spite of roentgen-ray treatment. In all cases the treatment was in moderate amounts, averaging about 1500 r (air dose) to each of two fields. No significant alteration in the character of the tumor in the roentgenogram could be attributed to the growth effect alone.

Effect of Irradiation. The general effect of roentgen-ray treatment on the growth of the tumor has been mentioned in connection with the size of the lesion revealed in the roentgenogram. There are certain smaller changes that have been seen occasionally in the roentgenogram. In four cases more septa appeared as a result of roentgen-ray treatment. One pathological fracture healed after treatment. In five no effect was evident on production or destruction nor on the pattern of the tumor. As noted before, nine continued to enlarge in spite of treatment.

These findings indicate renal cancer metastatic to bone shows somewhat varying growth rates; that moderate amounts of roentgen-ray therapy exert little if any effect on the growth of this lesion; and finally, that a few cases may show slight treatment response in the roentgenogram, in the form of more septa.

Size. The smallest metastasis to bone measured about 1 cm. in diameter and represented one of many similar areas of cancer metastases. The largest tumor was 22 by 18 cm., and the average about 10 cm.

SUMMARY

This study indicates that metastases in bone from renal cancer show practically constant features of medullary origin, oval configuration, destruction of medullary and cortical bone, and the formation of a periosteous mass. There were no metastases in which production exceeded destruction in degree. When occurring in tubular bones, the position of the metastasis was always symmetrical or nearly so. The boundary of the metastasis can best be described as being fairly apparent in many cases. Pathological fractures occurred in about half the cases. A periosteal reaction was infrequent. The

growth rate seemed to vary considerably, and most metastases showed little or no effect roentgenographically following moderate amounts of roentgen-ray treatment. There was no significant predilection for any bone nor for any particular part of a bone.

It seems possible to divide bone metastases from renal cancer into three roentgenographic types: the lytic, the septate, and the patchy. The lytic was the most common, being found in twenty-seven cases; the septate, in six; and the patchy, in three. The lytic form is characterized by a predominance of medullary and cortical destruction over productive change; the septate, by approximately equal degrees of production and destruction with an internal pattern made up of dense septa forming loculations; the patchy form is evidenced by fine patchy areas of medullary bone destruction. Generally speaking, the lytic and the patchy types constitute the roentgenographic appearance expected in the majority of cancer metastases in bone, while the septate form was sufficiently dis-



FIG. 8. *Lytic type of metastasis containing a few septa.*



FIG. 9. *Lytic type of metastasis in unusual location. A little periosteal reaction and a few septa are present.*

tinctive to warrant assuming renal cancer to be the primary tumor.

Five of the twenty-seven lytic cases showed septa formation in a minor degree (Figs. 7, 8, 9). True, the septa were delicate, indistinct, and incomplete, and the prominence of medullary and cortical bone destruction meant that these five cases had to be classified in the lytic group. However, their resemblance to the septate form suggests that it might be justifiable to relate their origin to renal cancer.

DIFFERENTIAL DIAGNOSIS

The purely lytic types of renal cancer metastases have nothing specific in their roentgenographic appearance to distinguish them from metastases of other origin. The differential diagnosis in this group must therefore distinguish them from the primary bone tumors, certain infections in bone, or the histi-

ocytes. Generally speaking, differentiation from the primary bone tumors is the most important and in most cases a knowledge of the roentgenographic characteristics of a metastasis is sufficient in itself to make differentiation possible. The important points are knowledge of the existence of a primary malignant tumor, multiplicity, the ill-defined edges, the predominance of destruction over production, the scarcity of periosteal reaction, the oval shape, the lack of internal pattern, and the symmetrical tendency.

What has been said for the lytic form holds for the most part for the less common patchy type. There is, however, a somewhat greater tendency for the patchy type to resemble Ewing's tumor, primary reticulum-cell sarcoma of bone, and certain infections.

The differential diagnosis of the septate form deserves special emphasis. We believe it is probably this form that has been responsible for the variety of roentgenographic diagnoses offered in renal cancer metastatic to bone. The resemblance to benign giant cell tumor of bone seems but a superficial one to us. Its asymmetrical position, absence of periosteal reaction, epiphyseal relationship, lack of soft-parts extension, frequency of fracture into the joint, the distinct periphery, and above all the internal pattern with its fine regular septation will differentiate giant-cell tumor. The roentgenographic characteristics of osteogenic sarcoma should enable one to differentiate it in most instances, for it is pear-shaped, shows a prominent soft-parts mass, and has plentiful periosteal reaction. Its borders are indistinct and often production predominates. The essential feature is the disorganization of the internal pattern with amorphous productive areas. Angioma of bone is an uncommon tumor in our experience. Its regular internal pattern, distinct periphery, absence of soft-parts mass, and absence of cortical destruction are some of the features that should distinguish it from the septate form of renal cancer metastatic to bone.

In our experience there are two conditions that somewhat resemble the septate form of metastasis. These are the large, partially loculated type of myeloma which occurs oc-

asionally and which has been reported as "solitary," and a few of the metastases of thyroid origin, especially the "metastasizing struma." The former has been seen in the flat bones. In both conditions the septa are less well developed, scanty, and incomplete with scalloping at the periphery of the tumor.

SUMMARY AND CONCLUSIONS

1. Thirty-six proved cases of bone metas-

tasis from kidney cancer have been studied roentgenographically.

2. Three forms of bone involvement have been noted: the lytic, the patchy, and the septate.
3. Recognition of the septate form in the roentgenogram offers the possibility of diagnosing the lesion as cancer metastasis of renal origin.

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GLANDLIKE ELEMENTS IN A PERIPHERAL NEUROSARCOMA

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THE occurrence of structures resembling glands capable of secretory function in peripheral nerve tumors appears to be quite rare. Comparatively little discussion on this subject has appeared in the literature, and the histogenesis of such elements remains in doubt. The following description of a glandlike, mucus-producing element in a neurosarcoma of the neck is presented, since it is the first such found in our material, and especially since the exact counterpart of this lesion has apparently not been previously observed.

CASE REPORT

E. L., an 8-year-old white girl, was admitted to Memorial Hospital June 22, 1945, for a swelling of the neck. The mother thought

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Received for publication, February 5, 1948.

the child had always shown a fullness in the left side of the neck.

In March, 1943, iodine drops had been prescribed for the patient, but the swelling did not recede. In December, 1943, when examined at another hospital, the mass in the left side of the neck had been found to extend anteriorly across the trachea to about the level of the thyroid gland. At that time a number of large, somewhat firm nodules were palpable in the left cervical region; a few nodules were noted on the right side and several "nodes" in the right axilla. Roentgenograms of the neck showed soft-tissue swelling and a slight deviation of the trachea to the right. Blood and urine studies, examination of sternal-marrow smear, intracutaneous tuberculin test, and roentgenograms of chest and neck showed nothing of importance. The clinical diagnoses that were considered included tuberculous (or other) cervical adenitis, thyroid cancer, and cyst.

Biopsy from the upper portion of the lesion on the left side of the neck furnished a report of plexiform neurofibroma. Subsequent com-



FIGURE 1.

plete skeletal roentgenograms showed little of significance. Additional physical examination revealed a few pigmented areas on her body and a small mass in the flexor surface of the right wrist. On later examination it was thought that some of the nodules had increased in size.

When she was admitted to Memorial Hospital on June 22, 1945, examination revealed a nodular subcutaneous mass in the left side of the neck, beneath the sternocleidomastoid muscle and extending deeply in the posterior triangle. The main portion of the mass was thought to be above the level of the clavicle.

Laboratory studies and a review of the submitted roentgenograms were essentially negative. The submitted slide from tissue previously excised was reviewed and a diagnosis of plexiform neuroma made.

On July 16, 1945, the tumor in the left lower neck was excised by Dr. Hayes Martin. At operation, it was found to be a hard, whitish, multilobulated tumor, firmly attached to the vertebral column, that extended upward to the base of the skull and downward to the superior mediastinum. Some of the branches

of the brachial plexus were identified and could be dissected free from the tumor, but it was impossible to identify the phrenic nerve; there was a question of its having been resected during the procedure. Using sharp and blunt dissection, the tumor was freed from the surrounding tissues posteriorly until the vertebral column was reached and superiorly up to the base of the skull. At this level it was necessary to cut through tumor.

The postoperative course was uneventful and the child was discharged from the hospital on August 1, 1945. On routine follow-up examination December, 1947, there was no evidence of recurrence of the growth.

PATHOLOGY REPORT

The specimen (Fig. 1) was described as being roughly cylindrical in shape, 11 cm. in length and 3 cm. in diameter, composed of interlacing cords, resembling nerve tissue, most of which varied from 3 to 8 mm. in diameter. The central mass was composed of adherent and partially confluent cords of



FIGURE 2.

such tissue, yellowish white and moderately firm, some measuring up to 2 cm. in diameter. A small amount of fatty tissue was adherent to the surface of the tumor.

Sections showed the bulk of the tissue to be a plexiform neuroma (Fig. 2) having the characteristic pattern of swirling interlacing bundles of narrow spindle cells with fusiform nuclei and scant pale-staining cytoplasm, and less regularly arranged, looser areas with longer, narrower cells having pinkish cytoplasm. In some areas the dense swirling tissue showed marked cellularity (Fig. 3), however, while in the looser regions (Fig. 4) some cells were pleomorphic tumor giant cells containing as many as ten nuclei, so that a diagnosis of neurosarcoma originating in a plexiform neuroma was made.

The principal feature of interest was a group of glandlike structures (Fig. 5) in the central tumor mass. These lay well within

the tumor on the border between a dense swirling area and a looser region as previously described. Serial sections revealed only one such group, and in all the sections in which it was found, it lay in an area almost encompassed by a single low-power field. Since these structures were essentially tubular, lined by columnar or cuboidal epithelium, they will be termed "glands" in the following discussion for the sake of brevity. There were three well-demarcated glands but in some of the sections smaller elements lay adjacent to these, so that a single section contained as many as twelve. The smaller ones were about the size of an intestinal gland, while the larger structures were cystic but with similar lining epithelium. The lumina contained a slightly basophilic amorphous material resembling mucus. The lining epithelium varied from cuboidal to high columnar and was without demonstrable cilia.

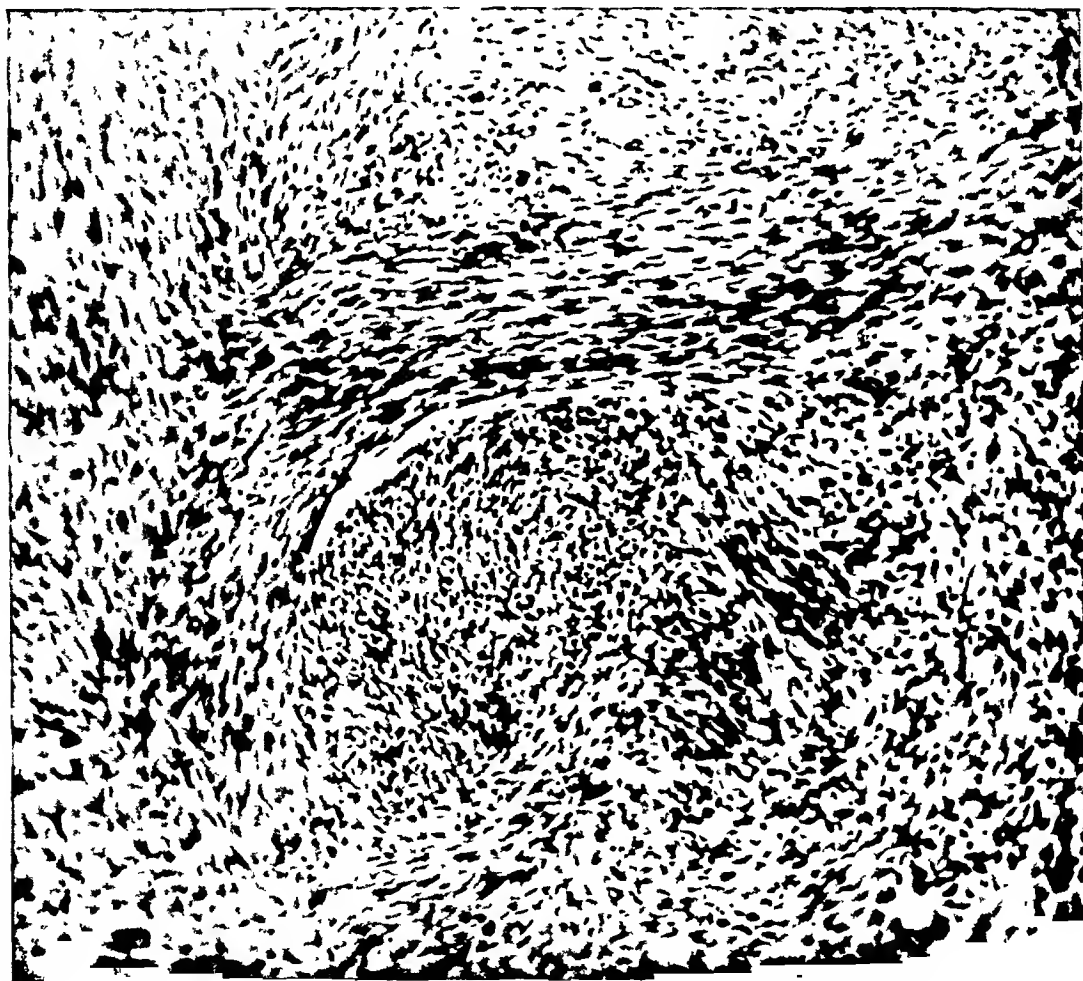


FIGURE 3.

A few of the cells resembled goblet cells, being distended by a material similar to that lying within the gland lumina, but most showed no evidence of secretory activity. Mucicarmine stain demonstrated the material within the lumina and within the goblet-like cells to be mucus.

The nuclei of the cells varied considerably in appearance; most were rather large with scant chromatin and a single small dark nucleolus, but some were much smaller and more deeply stained. Mitotic figures were not prominent. In some areas the nuclei were heaped up and, since the cell outlines were not clear, it is possible that many of the cells were multinucleated.

Some of the larger cystic structures showed areas of infolding lining epithelium, while other groups of smaller glands appeared confluent. The glandlike structures were well demarcated from the surrounding neuroma-

tous tissue which showed no variation from that more remote from this area; hence there was no evidence of a transition from glandlike to neuromatous tissue. Some of the smaller structures were poorly formed and suggested the appearance of outgrowths of the larger glands invading the neuromatous tissue. The normal human tissue which these structures most closely resembled was intestinal or respiratory mucosa, and if they had been seen in a section where this origin could be assumed, a diagnosis of low-grade adenocarcinoma would have been difficult to exclude.

Also within the central tumor mass but about 1.5 cm. from the glandlike elements was a group (Fig. 6) of about thirty cells having a tendency toward polygonal outline, with small round nuclei and variable, slightly granular cytoplasm. These cannot be definitely classified but suggest somewhat the

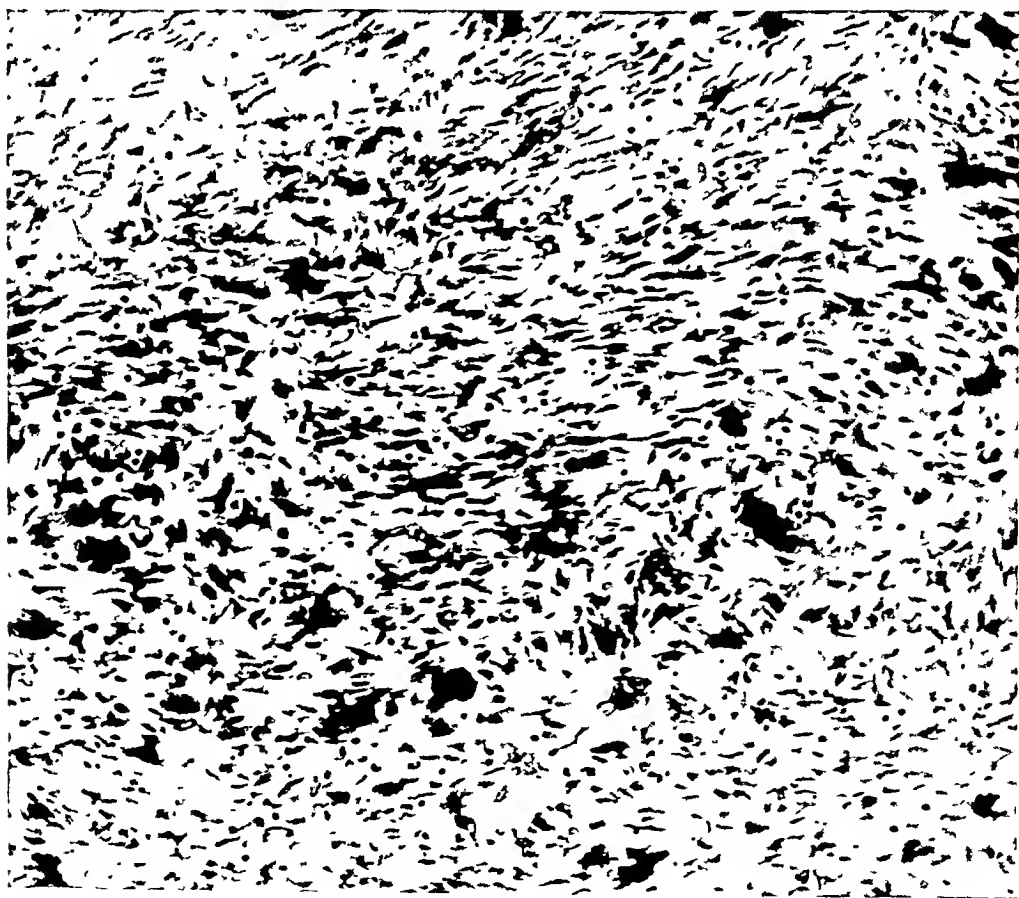


FIGURE 4.

appearance of nevus cells. They may be peripheral glial cells. They were not definitely demarcated from the surrounding neuromatous tissue, whose spindle cells were seen infiltrating among the polygonal cells.

DISCUSSION

Few case reports are found in the literature concerning the occurrence in peripheral nerve tumors of elements resembling epithelial structures, and the origin of such elements has not been determined.

Stout¹⁵ classified neurilemmoma, neurofibroma, neuroepithelioma and malignant neurolemmoma under neuroectodermal neoplasms. He stated¹⁸ that most malignant tumors of peripheral nerves are spindle-cell growths which in the past have been called fibrosarcomas, but indicated his belief that there are some grounds for believing that even these neoplasms may be of neuroecto-

dermal, instead of mesodermal, origin. In a previous comprehensive discussion of malignant peripheral nerve tumors¹⁶ he divided them into two groups: those that have the morphological characteristics of malignant fibroblastic tumors, and those that reproduce embryonal or adult neuroectodermal structures in a more or less recognizable form. He reviewed the reported cases and accepted the following three as being of this latter group.

1. In 1892, Garré reported the case of a 31-year-old female with von Recklinghausen's disease since youth, who developed a tumor in the left thigh, that, on excision, proved to be a fibrosarcoma made up of many small closely packed spindle cells. Just beyond the entrance of the sciatic nerve into the tumor, a large number of epithelial glands lined with a single layer of cuboidal epithelium were found. Recurrence developed in the amputation stump and death from local extension supervened in a few weeks.



FIGURE 5.

Garré speculated about the origin of these glands, rejecting a teratomatous formation for a more probable congenital displacement of the epithelium lining the neural tube. It was considered possible that the growth of the sarcoma may have excited proliferation of this embryonal rest to form the congeries of glands.

2. In 1918, Stout¹⁷ presented the case of a 42-year-old male, who developed a growth in the right forearm, followed in six weeks by the appearance of an axillary mass. Seven months after onset the growth was incised, following which it became painful and tender, while masses in the forearm and axilla rapidly grew larger. Nine months later interscapulothoracic amputation of the right upper extremity was done, and a long fusiform tumor was found enlarging the ulnar nerve from the elbow to the palm of the hand, together with metastases in the nodes, muscles, and nerves of the axilla. Seventeen days after operation there was an enlargement in the supraclavicular region and more metastases

developed. The patient died three months after operation. Autopsy showed tumor locally and in the thoracic wall as well as metastases in the cervical and mediastinal nodes, the pleura, and the lungs.

This very malignant tumor was characterized by a growth of masses of rather large rounded cells with many mitoses, which had invaded the tissues everywhere. The striking characteristic of these cells was the frequent formation of rosettes, composed of a concentrically arranged row of slightly elongated tumor cells about a tiny central lumen. The nuclei of these cells were oriented at the pole away from the lumen, and the cytoplasm at the internal pole of the cell contained exceedingly fine and closely packed fibrils that stained red with Mallory's aniline-blue-orange G stain and were arranged in a circular fashion forming a sharply accentuated border. Stout discussed the origin of these cells, suggesting that they might come from neuro-

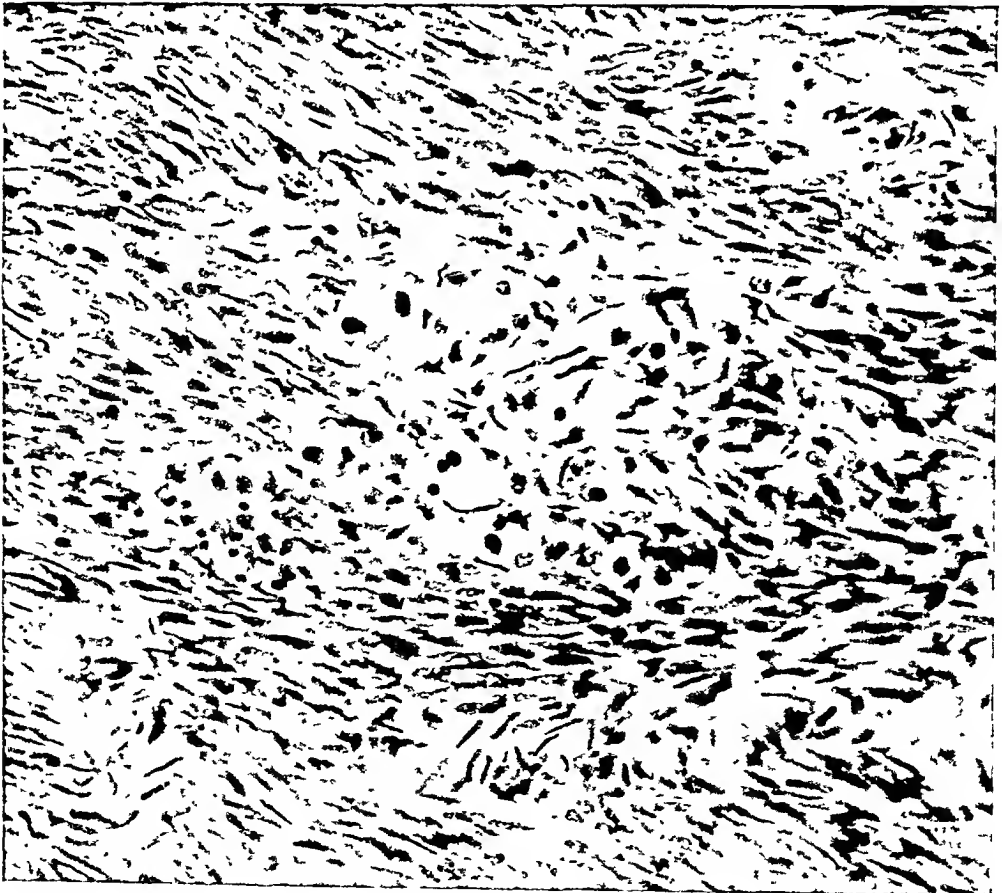


FIGURE 6.

cytes or from lemmocytes (embryonal peripheral glial cells); he favored the latter view. Penfield¹³ examined the material from this tumor and found some resemblance to the medulloblastoma of the central nervous system. His opinion was that: "It is an embryonic glioma of the periphery derived from cells which migrate from the neural crest to judge from the rosette formation. It seems to be true neuroepithelioma."

3. Cohn and Lanford and Cohn described the case of a 35-year-old man with von Recklinghausen's disease who, for six months, had had a tumor of the right median nerve that produced neurological symptoms referable to that nerve. The tumor recurred twice after excision; following this, amputation was performed. There were no further symptoms during the next four years. This tumor, like Garre's, was made up of spindle-shaped cells and epithelial elements. The epithelial elements were found again when the growth reappeared the first time, but the tumor was entirely sarcomatous when the arm was amputated.

The epithelial elements were composed of glands lined with columnar cells. Lanford believed that the growth resembled an ependymoma. Penfield¹³ examined material from this tumor, found the glands to be lined with several layers of columnar cells, showing no cilia or blepharoplast granules, and having no tails which passed outside of the basal membrane. He was uncertain whether or not the spindle cells forming the main bulk of the tumor were of neuroepithelial derivation.

Stout¹⁶ discussed cases reported by Bergstrand, Brandes, and himself but considered the evidence insufficient to classify them as neuroectodermal. Concerning another case reported by Cohn, Stout stated that analysis of the record forced one to suppose that the primary growth was probably in the lung and that the radial nerve tumor was a metastasis.

Other discussions of peripheral nerve tumors, such as that by Penfield,¹⁴ in general cover the same cases reviewed by Stout.¹⁶ In a discussion of peripheral neurogenic tumors, Foot noted the occurrence of glandlike epithelial structures in malignant neurinomas but described no specific cases. In a discussion of chest tumors derived from elements of the nervous system, Andrus¹ reviewed a case

previously reported by himself² in which a pathological diagnosis of neuroepithelioma of the lung was made in the case of a 23-year-old female with a lung tumor the size of an egg in the apex of the right lower lobe. Microscopic examination showed tumor masses of cells with small amount of stroma, little cytoplasm, round nuclei, and no mitoses. This description does not suggest true gland formation; neither do the published photomicrographs of this case. In a comprehensive review of spinal-cord tumors, Kernohan⁹ mentioned, in connection with neurofibroma, the tumors described by Stout^{16, 17} and Lanford and Cohn as specific tumors of peripheral nerves that simulate medulloepithelioma or medulloblastoma and are sometimes referred to as neuroepithelioma. Kernohan stated that none of these tumors has been found or described as having occurred within the vertebral canal.

Hackel reported a radial-nerve tumor made up of cuboidal epithelium resembling that of the medullary canal with rosettes, pseudoadenomatous structures resembling loose glial tissue, and areas of undifferentiated syncytial tissue. Stout and Murray¹⁸ discussed the case of a 35-year-old man who developed a tumor within the right radial nerve. The tumor was resected eight months after the appearance of pain in the arm, and eight months after resection, roentgenograms showed lung metastases. The radial-nerve tumor was composed of relatively small cells, variable round, polygonal, and short spindle-cell forms, having no differentiation, rosettes or pseudorosettes. In tissue culture, the tumor cells exhibited the growth characteristics of early, undifferentiated, embryonic epithelium. They felt that it was logical to interpret this as neuroepithelium and to classify the tumor as a neuroepithelioma.

The present case would not seem to correspond exactly to any of those found in the literature, although two of the cases considered by Stout¹⁶ also had other stigmata of von Recklinghausen's disease. His cases had gland formation with cuboidal or columnar epithelium but apparently did not have the active secretory function suggested in the present case.

On the basis of present evidence it is not possible to do more than speculate as to the origin of the glandlike elements. In discussing a somewhat analogous problem, the origin of cysts of the spinal cord lined by columnar cells with cilia, with actively secreting mucous and serous glands, Kubie and Fulton advanced four possibilities:

1. The least likely was considered to be an entodermal vestige, with implantation of entoderm in the spinal cord. The possibility of entoderm having a role in the origin of the mucus-producing glandlike elements in the present case must be considered, but its likelihood would appear exceedingly remote. A review of such a possibility with competent authorities in the embryologic field has yielded no support in this direction.

2. During closure of the neural tube, cysts, formed by a fortuitous infolding of ectodermal cells, might give rise to these lesions. Kubie and Fulton felt this explanation unlikely in their cases because ordinary dermoid or epidermoid cysts of the central nervous system are lined by stratified squamous epithelium. This would also reduce the likelihood of such a mechanism applying in the formation of a glandlike structure in a peripheral nerve in the present case.

3. The direct connection of the cysts with the surface of the cord in their cases sug-

gested to Kubie and Fulton that these may have arisen by an extramedullary outpocketing of the central canal, forming an extramedullary syringomyelia, but it was felt that this explanation failed to account for the presence of mucous and serous glands. Subsequent studies by Kernohan¹⁰ have indicated, however, that certain types of ependymomas contain intra- and extracellular mucus, so that an ependymal origin of the glandlike element in the present case is the most likely supposition. The fact that the tumor lay close to the vertebral column might be considered as favoring ependymal derivation.

4. Kubie and Fulton considered that perhaps any type of fetal epithelium, whatever its origin, might develop columnar epithelium possessing cilia under special unknown circumstances. If so, the effort to find close analogies in adult tissue is obviously useless. A generalization of this sort might apply equally well to the present case and can certainly neither be proved nor disproved on the basis of this material. Kubie and Fulton felt themselves unable to make a choice among these possibilities. Similarly it is not possible to ascribe a definite origin to the glandlike elements found in the neurosarcoma described here. The assumption is that one is dealing with an ependymal heterotopia.

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REPORT ON THE ILLINOIS CANCER BULLETIN*

Analysis of a Success

ERICH SACHS, M.D., REUBEN L. LARSEN, M.D., and A. C. IVY, PH.D., M.D.

THIS is the story of a co-operative endeavor to provide gratuitous and unsolicited medical education in a special field—the control of cancer. The project was sponsored by the Illinois State Medical Society; Illinois was the testing ground; the physicians in Illinois were the recipients of the formulated venture and the judges of its validity. The approach was unorthodox, but successful beyond expectations. Because of the exceedingly salutary results achieved by *The Illinois Cancer Bulletin*, a condensed report of its origin and development, together with mention of some of the editorial methods used, is herewith presented.

The objective of the *Bulletin* was reduction of cancer mortality. The publications were copyrighted to guard against their misuse, but permission has been freely given to quote from them, imitate them, distribute them widely, and even to republish them under the masthead of other states. It is the considered view of the sponsors that if *The Illinois Cancer Bulletin* serves to encourage similar efforts on the part of other responsible organizations another desideratum will have been realized.

ORIGIN

In July, 1945, in Chicago, a small group of men convened under the auspices of the Committee on Cancer Control of the Illinois State Medical Society. The object of the meeting was to devise methods for reducing cancer mortality. It was determined to publish a series of bulletins that would, through repetition and emphasis, implant the thought in the

minds of physicians that *early cancer is curable*. Early diagnosis and adequate treatment without undue delay were defined as essential features for cure and control. Inasmuch as the general practitioner is of primary importance to the success of such a campaign it was agreed to direct the effort specifically at him without, however, excluding any of the 11,000 physicians in Illinois.

Consideration was given to the probable and possible causes of failure in previous attempts of a similar nature. It was concluded that mere publication of a discourse, regardless of its importance or the quality of its content, is not enough to assure its reading and application. Reader acceptance, particularly when sustained interest is required, depends to a great extent, strange though it may seem, upon apparently trivial and incidental matters: visual impression, clarity and organization of the typography, color, illustrations, and the amount of material presented in a single issue. Failure to consider any of these items might lead to failure of the whole project.

Realistically, the reader was visualized as a physician after a long day's work, swamped with medical literature—professional and promotional, much of it in outstandingly attractive "makeup"—confronted with another bulletin to read. In the face of such competition, it was realized that the projected publication must present an immediate and strong appeal.

On the basis of this reasoning it appeared advantageous to utilize the experience of men who possessed first-hand information about the psychologic factors influencing the physician as a reader of medical literature, and to employ methods of proved efficacy for compelling reading interest. The central theme—*early diagnosis*—was regarded as a commodity which would have to be sold; the problem

* Rendered possible financially by a grant from the National Advisory Cancer Council of the U. S. Public Health Service, the Illinois Division of the American Cancer Society, and L. G. Maison and Company of Chicago.

Received for publication, January 15, 1948.

was how to gain, maintain, and test the readers' interest.

THE TEXT

It was decided that the text should consist of two principal compelling themes, not separately treated but inextricably interwoven wherever possible.

First, the negative attitude of defeatism, the assumption that cancer is incurable, must be counteracted, and a spirit of optimism be created. The slogan, "EARLY CANCER IS CURABLE," was adopted for inclusion in the masthead of every issue. The opening number was to show the magnitude of the cancer problem and the appalling inroads it is making in our lives, emphasize the great responsibility of the physician in the campaign against the scourge, and challenge him to save tens of thousands of lives every year through awareness of the problem, alertness in recognizing early evidences of the disease, and promptness in application of adequate treatment.

Cognizance was taken of the fact that such a positive attitude might foster unwarranted optimism. It was felt, however, that the prevailing pessimism called for strong counter measures, and that the text would dispel any tendency to unrealistic and undue optimism.

Second, the body of the text was to recall to the readers the recognized tools and methods for early recognition of cancer, all carefully selected for their applicability in *every-day practice*. Didactic presentation would be necessary, but the burial of salient points in a grave of circumlocution must be avoided. When details might be necessary they should be limited to the requirements for applicability of the method.

All of the diagnostic means are not in the hands of the general practitioner. For this reason, it was decided to give particular attention to "indications for consulting a specialist," and to indicate the possibilities for earlier diagnosis through the utilization of specialists and their refined diagnostic aids. Contributions from specialists were also envisioned, to allow them to state their ease, create a better understanding, and emphasize the urgent need for early co-operation, before the

disease will have had time to reach an advanced stage.

At this point it seems timely to insert a word of praise for the contributors of special articles. Those who contributed to the last few numbers of Volume I—the volume giving the over-all picture of cancer in its protean manifestations—were required to have their papers published anonymously in the interest of the cause. All contributions—in Volumes I and II—were subjected to revision, curtailment, and other changes, at a sacrifice of personal distinguishing quality, in the interest of homogeneity of editorial thought and diction. In order to safeguard this homogeneity even further, no special editorial board or directing committee was set up. After approval of the program as a whole by the Committees on Cancer Control of the Illinois State and Chicago Medical Societies and by the Chicago Committee of the American Society for the Control of Cancer, the only control exercised over the text was that of a few members of the Committee on Cancer of the Illinois State Medical Society. These specialists limited their function to correction of possible factual errors and to assistance in formulation of the text in controversial matters.

PLANNING, APPEARANCE, AND TIMING

The basic plan was to organize the material into sections, each section to form one bulletin, one bulletin to reach every physician in Illinois every two weeks for a period of six months. It was believed that a series of bulletins thus released would stand a better chance of being read than a single book into which all the material was incorporated. It was also decided to present the bulletins in such a form that the total of 13 individual issues, punched for filing, could eventually be made into a handy booklet for future reference. The "shelf-life" of the bulletin, however, was a point of secondary importance.

Each bulletin consisted of six pages of letterhead size ($8\frac{1}{2} \times 11$ inches). A smaller format would have made it look unimportant: a larger one would have been inconvenient, and the six-page size carries an amount of copy that can easily be read in one sitting—an

important point. A little psychologic "trick," to arouse the reader's curiosity, went into the six-page format: the fifth page folded over the third, concealing the contents of this page and interrupting the continuity of the text.

Each bulletin was a self-constituted unit with specific topics for discussion. Following a generalized discussion of the cancer problem in the first two bulletins, consideration was given to early diagnosis by organs and systems.

At the end of each bulletin the subject of the next issue was announced, to arouse interest in what was to follow.

Much consideration was given to the visual appearance of the printed page. Above all, monotony had to be avoided; this suggested the free use of color. Color was employed in the type by setting main heads in red. The campaign slogan "EARLY CANCER IS CURABLE," appearing in the masthead, was also in red, as well as two secondary slogans running across the tops of pages 2 to 6: "When The Patient Is Over Forty, Think Of Cancer First" and "When The Patient Is Under Forty Think Of Cancer, Too." Whenever possible, colored illustrations were used.

The copy itself appeared in two columns, to reduce the length of the lines. Subdivisions in great numbers interrupted the even flow of the text, supported by heavier print to introduce paragraphs.

Important matter within the copy was emphasized by boldface type. Since regular use of this method might promote "short-cut" reading, it was not employed routinely; in some instances, only such words as led to important points were emphasized.

The instruction and attention value of illustrations was utilized as far as feasible; limitations were imposed by the scarcity of material on early cancer. Many illustrations of cancer in advanced stages, where the appearance is unmistakable, were available, but it was felt that prominence should not be given to such illustrations in discussions devoted to *early diagnosis*. Their incorporation could not be avoided entirely, however.

The appearance as a whole was designed to make the *Bulletin* look important and dignified, but an effort was made also to bring it near to the reader's heart. The physicians of

Illinois were asked to realize that the bulletins were written by men like themselves, striving for practical information. In order to promote the feeling that the *Bulletin* was their own, anonymity of the presentations was considered an essential feature. An appeal to local pride was made by calling it "*The Illinois Cancer Bulletin*," giving in the masthead the names of the men of their own Committee, and calling their attention to the fact that the effort was sponsored by their own state society.

EVALUATION OF INTEREST

After all these ideas had taken concrete shape in the first volume, it appeared desirable to test their soundness.

Interest in a book is easily gauged by its sale. Interest in printed matter that is provided gratuitously cannot be evaluated accurately; it can only be estimated through special devices. A postcard (with no postage required) was enclosed with the first bulletin; another was enclosed with the last. The first card carried a printed request for a binder to make a permanent file of the bulletins which would follow. This was a free offer. The card enclosed with the last bulletin asked those readers who desired to remain on the mailing list for a second volume to return their names and addresses.

The response to the first card was approximately 50 per cent, to the second, approximately 27 per cent. In tests of this kind a 10 per cent return is ordinarily considered excellent.

Conclusions from such tests must be drawn with caution. The only direct and real proof of the effectiveness of such a series of bulletins would, of course, be a reduction in the mortality rate from cancer, traceable to earlier recognition, in the area of distribution. Reply-card tests, such as mentioned above, do not prove that each bulletin has been read. They indicate, when the response is higher than customarily experienced, that a positive interest was present from the beginning, and that reader interest at the end of the first series was strong enough to justify a continuation of the effort.

Interest may also be gauged by complimen-

tary letters and notes received. A few physicians actually wrote that the bulletins had helped them to make an early diagnosis of cancer. Many physicians wrote letters expressing their appreciation for the useful information provided. Even more revealing were the many unsolicited and affectionate little notes of thanks and appreciation scribbled on the edges of the returned, preprinted mailing cards.

While all these responses pointed to the fact that the *Bulletin* had aroused the interest of physicians in Illinois, the favorable reaction was not restricted to this state. The mailing list included the Health Officers of all forty-eight states, the State Commanders and the Chairmen of State Executive Committees of the Field Army of the American Cancer Society, the Surgeon General's Office, the National Cancer Institute, and a number of physicians interested in cancer in many different parts of the country. From these readers, too, came a great many complimentary letters and congratulations.

While politeness cannot be discounted entirely in the evaluation of this type of reply, the fact that thirty-three states and territories ordered the *Bulletin* for distribution to the physicians of their respective states, and that many more requests are pending, proves that *The Illinois Cancer Bulletin* was more than a local success. The *Bulletin* was made available at cost to any state organization desiring it, printed under its own state masthead. Many complimentary letters were received from these sources, too.

Within six months after the publication of the *Bulletin*, the interest in the establishment of Cancer Clinics in hospitals in the State of Illinois increased. Likewise, the use of the established clinics and the biopsy specimens received for examination were definitely augmented. This cannot be attributed to the influence of the *Bulletin* alone, since, unfortunately from the viewpoint of a controlled experiment, the campaign of the American Cancer Society and increased activity of the Cancer Control Department of the State Health Department undoubtedly contributed a great deal. However, all consult-

ants agree that the issuance of the *Cancer Bulletin* by a Committee of the State Medical Society definitely facilitated the efforts of these other groups.

FINANCING

It may be misleading to report on the topic of financing under the heading "analysis of a successful experiment." The money made available through the National Advisory Cancer Council and the Illinois Division of the American Cancer Society barely covered the expenses of printing, typography, artwork, engraving, mailing service, postage, and so on. The publisher donated his services (the lion's share of the expense). The color plates were made and placed at the disposal of *The Illinois Cancer Bulletin* by a pharmaceutical house, without cost, a saving of approximately \$4000.00.

Retrospectively, the confession must be made that a clear anticipation of the magnitude of the financial problem—provided everything had to be paid for by the society—would probably have led to abandonment of the plan.

OUTLOOK

The success of the first volume of *The Illinois Cancer Bulletin* demonstrated the need for this type of publication. A second volume, twelve bulletins abridged to two pages each, highlighted the problems of differential diagnosis in various systems and organs. Continuation is not possible because of the expense involved.

A thorough and critical discussion of recently introduced methods for early cancer diagnosis would be valuable. The highly controversial topic of adequate therapy should be presented in such a manner that the general practitioner would get a clearer concept of his role in this picture. Many other aspects of practical importance need to be covered.

It would be most gratifying to those who produced *The Illinois Cancer Bulletin* if their efforts should serve as a stimulus to other organizations who might be in a position to continue the work, so that their experiment could be effectively utilized on a larger scale.

CURRENT *Cancer* LITERATURE

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GENERAL

Ackerman, Lauren V., & Regato, Juan A., del: **Cancer: Diagnosis, Treatment, and Prognosis.** St. Louis. C. V. Mosby Company. 1947. 1115 pp. \$20.00.—In the opinion of the reviewer this book represents a major contribution to the useful literature on neoplastic diseases. Seldom, if ever, can a reviewer find himself in agreement with every statement made by others, for experiences must differ with different individuals, and exceptional interests and experiences in specific fields of endeavor must always lead to ideas rarely expressed to one's satisfaction by authors who treat of diseases in toto. It is not my belief that a review should content itself with disagreements in minutiae for such always exist.

In a survey of this work three things impress me: (1) the completeness of the production, (2) its usefulness to the practitioner in the cancer field, irrespective of his particular "specialty," and (3) the fact, which must be obvious to anyone familiar with the subject, that this book is written on the basis of large personal experience and is not merely something which has been copied from pre-existing works. Perhaps the favorable impression made upon the reviewer is so pronounced because so many of the statements contained might have been his own and made to students in his own laboratory. The experiences which make up the text of this work coincide on the whole very closely with those of the reviewer and the divergences in experience are few. If any criticism were to be expressed it would be that there are too many photographs which show *big* cancers and not enough which show the cancers at the stage the clinician ought to want to see them. What medicine needs is more *little* cancers.

The scope and comprehensiveness of this text are indicated by the chapter titles: *Part I*: I. Introduction; II. Cancer Research; III. Pathology of Cancer; IV. Surgery of Cancer; V. Radiotherapy of Cancer. *Part II*: VI. Cancer of the Skin; VII. Cancer of the Respiratory System and Upper Digestive Tract; VIII. Tumors of the Thyroid Gland; IX. Tumors of the Mediastinum; X. Cancer of the Digestive Tract; XI. Cancer of the Genitourinary Tract; XII. Cancer of the Male Genital Organs; XIII. Tumors of the Suprarenal Gland; XIV. Cancer of the Female Genital Organs; XV. Cancer of the Mammary Gland; XVI. Malignant Tumors of Bone. XVII. Sarcomas of the Soft Tissues; XVIII. Cancer of the Eye; XIX. Hodgkin's Disease; XX. Leucemia.—F. W. S.

Bortz, Edward L. [Univ. Pa. Grad. Sch. Med., Philadelphia]: **Cancer: a biologic problem.** Postgrad. Med. 3: 1-7, Jan., 1948.

Glaser, Hugo [Vienna, Austria]: **Krebs und Allergie.** [Cancer and allergy.] Krebsarzt 3: 27-29, Jan., 1948.—The author reports a case which seems to him to support the contention, as well as reported data, that cancer is an allergic manifestation.—M. C. J.

Gould, Sue Thompson: **Cancer education.** M. Woman's J. 55: 25, Apr., 1948.

Hambrecht, Fred, & Crowell, E. A. [Galesburg, Ill.]: **Continuity metastases.** Illinois M. J. 93: 38-41, Jan., 1948.

Hargreaves, W. H. [Office Surgeon Gen., U. S. Army, Washington, D. C.]: **Some present trends in American medicine.** Practitioner 160: 46-52, Jan., 1948.—Includes a subsection, "The Cancer Campaign."

Hartz, Ph. H.: **Algunos datos de la presencia de cáncer en la población indigena de Curaçao, I. N.** [Data concerning the incidence of cancer in the indigenous population of Curaçao, I. N.] Rev. sudam. morfol. 5: 108-111, Dec., 1947.—This survey of cancer incidence in Curaçao from 1936 to 1947 is based upon findings in 1803 autopsies out of a total of approximately 7600 deaths. Of the autopsies, 1608 were on Negroes or "people of color," the remainder on Chinese, Syrians, Venezuelans, Europeans, etc. Cancers were found in 166. They occurred in 8.7% of males and 12% of females. The greatest incidence was esophageal cancer both in males and females, and [contrary to what is observed in the U. S. A.] the incidence in the sexes was approximately equal. Stomach and lung followed in males; cervix, stomach, ovary, breast in females. The incidence of prostatic cancer was very low—but 3 of 78 cancers in males. Comparison is made with figures based on autopsies in Panama on Negroes from the British West Indies. There gastric cancer came first, next prostatic, and third esophageal. A high incidence of the latter disease in females was not observed. In both the Panama and the Curaçao figures, esophageal cancer is 8 to 10 times as frequent as in those based on Negro autopsy figures from the state of Tennessee.—F. W. S.

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- Taylor, Grantley W. [Harvard M. Sch., Boston, Mass.]: *Cancer*. *New England J. Med.* 238: 598-602, Apr. 22, 1948.—An outline of recent progress in: education; detection; diagnosis; knowledge of lymphatic spread; surgical treatment of various cancers.—*D. A. S.*
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- Aud, Guy [Kentucky Div., Am. Cancer Soc., Louisville]: The cancer mobile unit. *Kentucky M. J.* 46: 75-76, Mar., 1948.—In order to bring facilities for the diagnosis of cancer directly to the citizens of certain areas of Kentucky where there are too few doctors and hospitals, a self-contained mobile unit for the diagnosis of cancer was constructed. It contains complete diagnostic x-ray equipment with development tank, sterile instruments and supplies for the removal of tissue for biopsy, instruments for bronchoscopic and sigmoidoscopic examinations, and a small laboratory for microscopic examinations. All tissue examinations are made by members of the Kentucky Society of Pathologists, without charge. There is a dressing room for patients, folding tables for filling out clinical records, and adequate storage for records and supplies. There is indirect lighting, and heating is by electricity. A small, permanent staff is in charge. The services of the mobile unit are arranged for a community by invitation of and in co-operation with the County Medical Society.—*D. A. S.*
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- McLean, Jay [Bur. Cancer Control, Health Dept., Washington, D. C.]: District cancer control. *M. Ann. District of Columbia* 17: 59-61, Jan., 1948.—With a cancer detection examination every six months, 500,000 examinations would be required in the District of Columbia annually. This would average 500 examinations a year for each available physician. A full-time physician in a clinic all year could do possibly 2,500 examinations. The District would thus require a total of 200 clinics with full-time physicians and nursing staffs. The entire United States has less than 500 cancer clinics and most of them are in operation only 1 or 2 days a week. Cancer detection clinics function in an educational capacity, and the required number for a complete program of examinations is impracticable; hence, the control of cancer is the responsibility of every physician.—*J. M. Sether, M.D.*
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Viruses and cancer. *Practitioner* 160: 124-128, Feb., 1948.

Körbler, Juraj [Zagreb, Yugoslavia]: Über die Entstehung bösartiger Geschwülste im unmittelbaren Anschluss an einmalige Verletzungen. [Occurrence of malignant tumors immediately following a single injury.] *Krebsarzt* 3: 102-104, Mar., 1948.—Of 10,000 patients treated between 1931-1947, 3 appeared to have malignant tumors following an injury: a squamous carcinoma following a blow to the head with subsequent irritation by combs; basal-cell epithelioma following skull wound by a shell splinter; partly pigmented basal-cell epithelioma of the nose following a blow.—*M. C. J.*

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Haddow Alexander [Middlescx Hosp., Eng.]: Paterson, Edith; ApThomas, Incz; Riches, E. W., & Boyland, E.: Discussion on chemotherapy in malignant disease. *Proc. Roy. Soc. Med.* 41: 45-51, Jan., 1948.

Hyndman, Olan R. [Denver, Colo.]: Intractable pain due to cancer. Treatment by neurosurgical methods. *Am. J. Surg.* 75: 187-199, Jan., 1948.—In patients with cancer, pain is produced in various parts of the body by mechanical effects of the growth: obstruction, infiltration, compression, primary and metastatic tumefaction, and secondary inflammation. Neurosurgery is re-

quired chiefly for advanced primary cancers of the uterus and cervix, breast, buccal cavity, and their metastases. Narcotics, irradiation, and sex hormones for the relief of pain in inoperable cancer are usually considered and tried before neurosurgery. Morphine is the "first court of appeal" when pain becomes manifest and, when neurosurgery is not advisable, it or a substitute may be the sole means of palliation. It may also be used with irradiation and neurosurgery. Irradiation may produce considerable palliation and the author feels that the radiologist at least should be consulted before neurologic surgery is undertaken. In some instances, sex-hormone therapy should be tried.

Neurosurgery should be the "last court of appeal" but should not be delayed unnecessarily. The neoplasm must be histologically identified and a state of inoperability established beyond question. If a highly malignant, rapidly growing neoplasm is present in an extremely debilitated patient, narcotics may well add more total palliation than neurosurgery. Once an operation for intractable pain is indicated, a procedure designed to give definite results should be chosen—"except for pain in the face and throat, a section of the spinothalamic tract at an appropriate locus is the procedure of choice at the present writing." The use of subarachnoid injection of alcohol has been limited and of little benefit. Its chief application has been to the thoracic nerves and in cases of pain due to causes other than cancer. Rhizotomy is the method of choice only for pain in the face, tongue, mouth, and throat. Sympathectomy has no place in the treatment of pain due to cancer with the one exception, presacral neurectomy, which usually is used along with some other procedure.

The surgical procedure of choice for pain in the face, mouth, tongue, throat, and neck is transection of the root of the fifth nerve by either the subtemporal or occipital route. Sjöqvist's (1938) trigeminal tractotomy is not successful.

Relief of pain in the shoulder and upper extremity, most frequently due to metastatic cancer of the breast, presents the greatest difficulty. Section of the brachial plexus or its intraspinal roots produces a paralyzed extremity, the adjustment to which is difficult for the patient, and phantom pain or sensation sometimes persists. High cervical chordotomy is fraught with danger—particularly respiratory embarrassment—fails to relieve pain satisfactorily, and has no specific value according to the author. Instead, for analgesia as high as D-1 or D-2 or higher, he recommends section in the medulla, above the cervical danger zone, as described by Schwartz and O'Leary and by Adams and Monro; or mesencephalic tractotomy as described by Walker.

Chordotomy has proved entirely satisfactory for effective analgesia below the level of D-5 or D-6. Untoward symptoms do occur, more consistently when bilateral procedures have been performed: weakness of the lower extremities, atony of the bladder and weakness of bladder and bowel sphincters, loss of ability for orgasm,

and permanent and severe orthostatic hypotension. Recovery usually takes place quickly and to a considerable degree. The author suggests the term *spinothalamic tractotomy* with the level designated, e.g., spinal. The author has had no experience with prefrontal leucotomy but he believes that it may produce results more desirable than the methods he has described.—*S. A. Wilkins, Jr., M.D.*

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Martin, Hayes [Memorial Hosp., New York City]: Instruments useful in head and neck operations. *Ann. Otol., Rhin. & Laryng.* 56: 1021-1028, Dec., 1947.

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Warren, Shields [Boston, Mass.]: The radiosensitivity of tumors. *Rocky Mountain M. J.* 45: 205-206, Mar., 1948.—A review.

Wegelius, Carl [Wihuri Res. Inst., Helsingfors, Fin.]: Capacitive electric charge as a biologically active element in roentgen treatment of organic tissue. (Preliminary report.) *Acta radiol.* 28: 468-473, Nov., 1947.

Winternitz, Jan G. [Roy. Cancer Hosp. (Free), London, Eng.]: Carcinoma of the cervix: a discussion on the value and techniques of supplementary x-ray therapy. *Brit. J. Radiol.* 21: 27-40, Jan., 1948.

RADIOACTIVE ISOTOPES

Bloch, Konrad, & Anker, H. S. [Univ. Chicago, Ill.]: An extension of the isotope dilution method. *Science* 107: 228, Feb. 27, 1948.

Govaerts, J.: La désintégration de la matière et ses applications biologiques. [Disintegration of matter and its biological applications.] *Rev. méd. Liège* 2: 553-560, Oct. 15, 1947.—Review of isotopes.

Halin, P. F.; Goodell, J. P. B.; Sheppard, C. W.; Cannon, R. O., & Francis, H. C. [Vanderbilt Univ., Sch. Med., Nashville, Tenn.]: Direct infiltration of radioactive isotopes as a means of delivering ionizing radiation to discrete tissues. *J. Lab. & Clin. Med.* 32: 1442-1453, Dec., 1947.—Direct infiltration of neoplastic tissues was attempted with gold colloids insoluble in body fluids. They contained about 3 mc./ml., by the authors' estimate. Following infiltration, measurements were made with a directional counter to determine localization. Good results were obtained in the treatment of enlarged lymph nodes in Hodgkin's disease, and of a supraclavicular mass in a man with lymphosarcoma who received about 19 mc. over a period of a month. Subcutaneous lesions in a patient with chronic lymphocytic leukemia had regressed a week after about 1 mc. in 0.3 ml. of sol was injected, while topical application of about 1 mc. in place for 3 days caused desquamation of several other lesions, leaving normal-appearing skin. Gold sols given intraperitoneally in 2 cases were retained in the peritoneum. In a vascular scalp lesion metastatic to a hypernephroma, the injection did not remain localized, but resulted in an effect similar to an intravenous administration. Lack of retention was seen in a squamous cancer of the vagina, due to the ex-

- treme friability of the mass. In such a case, the possibility of using AgNO_3 , where the caustic action might fix it to the tissue, is discussed.—*E. F. Focht, B.A.*
- Heilig, Robert [Lady Willingdon Hosp., Jaipur, India]: Medical aspects of atomic energy. *Indian Physician* 7: 1-10, Jan., 1948.
- Maxfield, J. R., Jr., & Maxfield, Jack G. S. [Dallas, Tex.]: The use of radioactive isotopes in diagnosis and therapy. *Texas State J. Med.* 43: 558-562, Jan., 1948.
- Muller, J.-H. [Univ. Zurich, Swt.]: Contribution à l'étude du métabolisme du zinc, par la méthode des indicateurs radio-actifs (utilisation de l'isotope radio-actif artificiel Zn^{65}). [The study of metabolism of zinc by means of radioactive indicators (utilization of artificial radioactive isotope Zn^{65}).] *Bull. schweiz. Akad. d. med. Wissensch.* 3: 56-66, Nov., 1947.—Using radiozinc (Zn^{65}) in the chemical form of its sulfide, as a radioactive tracer, and working with rats, the author has studied the excretion and distribution of zinc in the organism after intraperitoneal, intramuscular, and intravenous injection. By the methods used, namely the measurement of specific radioactivity and autohistographic examination of the tissues, it has been established that the zinc tends to be excreted rapidly by the organism after intramuscular and intravenous injection and more slowly after intraperitoneal injection, owing to the fact that persistent deposits are formed within the peritoneum. This peculiarity may be considered favorable in view of the use of radiozinc (mixture of isotopes Zn^{65} and Zn^{67}) in the form of intraperitoneal injections in cases of carcinosis of the peritoneum, according to the therapeutic directions previously published by the author.—*Auth. Summ.*
- Pace, Nello; Loevinger, Robert, & Strajman, Enrique [Univ. Calif., Berkeley]: In vivo Geiger-Müller gamma-ray counter for radioisotope distribution studies. *Science* 107: 71-73, Jan. 16, 1948.—A compact γ counting tube has been developed for in vivo determinations in man. A Cu or brass tube body with $\frac{1}{16}$ in. wall serves as the cathode. The inner diameter of the tube is $\frac{7}{8}$ in. and outer length 1 in. A Cu disk, $\frac{1}{16}$ in. thick and 1 in. in diameter acts as the counting surface of the tube. The anode consists of a central 3 mil W wire. The counting voltage is 1000-1100 v., with a plateau 200-400 v. long at a slope of 2-3%/100 v. In the 1 in. Pb shield the background varies from 5 to 50 counts per min., but is constant for any 1 tube. The tube life appears to be of the order of 10^6 total counts, and the resolving time is $1.0 = 1.5 \times 10^{-2}$ min. A Ncher-Harper preamplifier stage is recommended. A Pb shield 1 in. thick, with a collimated length below the tube of 2 in., gave an angle of 47° for the counting field. Data show the counting rate for any source thickness in % of the maximum counting rate at infinite thickness for a 0.5 Mcv γ source homogeneously distributed. Simultaneous readings at various parts of the body were made by photographing the corresponding mechanical registers of several counters and a timing device.—*E. F. Focht, B.A.*
- Sheppard, C. W.; Goodell, James P. B., & Hahn, P. F. [Vanderbilt Univ. Sch. Med., Nashville, Tenn.]: Colloidal gold containing the radioactive isotope Au^{199} in the selective internal radiation therapy of diseases of the lymphoid system. *J. Lab. & Clin. Med.* 32: 1437-1441, Dec., 1947.—For internal radiation therapy of diseases of the lymphoid system, the radioactive isotope Au^{199} was found to be suitable as to half-life radiation, specific activity, cost, known chemical and biological behavior, and absence of long-lived contaminants and toxic effects. The preparation of stable colloidal suspensoid sols is simple. 4 mg. is the dose limit. The metallic gold is converted to a solution of gold chloride which is reduced once more to metallic gold in alkaline solution by adding ascorbic acid. The γ radiation of the doses was measured with a Lauritsen electroscope, using arbitrary units.—*E. F. Focht, B.A.*
- Stevens, G. W. W. [Kodak, Ltd., Wealdstone, Middlesex, Eng.]: Resolution testing in autoradiography. *Nature* 161: 432-433, Mar. 20, 1948.
- Tobias, C. A. [Univ. Calif., Berkeley]: Weymouth, P. P.; Wasserman, L. R., & Stapleton, G. E.: Some biological effects due to nuclear fission. *Science* 107: 115-118, Jan. 30, 1948.

ANATOMICAL REGIONS

- Goldstein, Albert E., & Rubin, Seymour W. [Sinai Hosp., & Hoffberger Urol. Rcs. Lab., Baltimore, Md.]: Multiple primary neoplasms. A summary of the literature and report of a case of four primary neoplasms with complete autopsy findings. *Bull. Sch. Med. Univ. Maryland* 32: 140-149, Jan., 1948.—Adenocarcinoma of sigmoid with metastases to liver; hypernephroma with metastases to right lung; basal-cell epithelioma of skin; and papillary carcinoma of bladder.—*M. C. J.*
- Gordon, Benjamin S. [Veterans Adm. Hosp., Bronx, N. Y.]: Triple synchronous primary carcinoma. *Arch. Path.* 45: 56-64, Jan., 1948.—Case report: adenocarcinoma of prostate with extensive metastases; epidermoid bronchogenic carcinoma metastasizing to cervical lymph nodes; and papillary adenocarcinoma of thyroid found at autopsy.—*D. A. S.*
- Maier, Herbert C. [Memorial Hosp., New York City]: Bronchiogenic cysts of the mediastinum. *Ann. Surg.* 127: 476-502, Mar., 1948.—Eight cases of bronchogenic cysts are reported and the literature reviewed. These cysts are now known to be one of the most common tumors of the mediastinum, and may be grouped as: paratracheal, carinal, hilar, paraesophageal, miscellaneous. They result from faulty development of the primitive foregut. The cyst wall resembles that of the bronchus. Some elicit no symptoms; the cyst is demonstrated only by a routine chest

x-ray. In general, symptoms are due to compression of the tracheobronchial tree; when infection supervenes, to intrathoracic suppuration. X-ray studies, angiocardiology, bronchoscopy, esophagoscopy, and aspiration biopsy (yields thick, white or yellow mucoid material) are used in differential diagnosis. Often diagnosis can be established only by surgical exploration. Surgical extirpation through a posterolateral approach is recommended if the patient's general condition permits. Partial removal is done if complete excision appears to be too hazardous. The author warns against injury to the tracheal wall. There were no operative deaths in the 8 cases: 7 had an uneventful convalescence. In 1, lobectomy was performed because the mediastinal cyst extended into a right upper bronchiectatic lobe. 1 was a girl, aged 8 mos.—*H. E. E.*

NECK

Dahleen, Henry C. [San José, Calif.]: Tumor of the carotid body. *South. Surgeon* 14: 264-272, Apr., 1948.

Donald, R. A., & Crile, George, Jr. [Cleveland Clin., Ohio]: Tumors of the carotid body. *Am. J. Surg.* 75: 435-440, Mar., 1948.—Report of 5 cases and discussion.

LeCompte, Philip M. [New England Deaconess Hosp., & Harvard Cancer Comm., Boston, Mass.]: Tumors of the carotid body. *Am. J. Path.* 24: 305-321, Mar., 1948.—According to present evidence, the carotid body is a chemoreceptor, not a gland of internal secretion, and not part of the "chromaffin system." In a series of 17 tumors of the carotid body no true chromaffin reaction was demonstrated, and no evidence for the secretion of epinephrine was obtained in assay of the fresh tissue in 2 instances. Tumors of the carotid body exhibit a basic pattern of nests of "chief" cells surrounded by a more or less vascular stroma. Depending on the relative amounts of "chief" cells and stroma, they may be described as "usual," "adenoma-like," or "angioma-like." Use of the noncommittal term "carotid-body tumor" is preferred to other names generally used. The great majority of these tumors are both histologically and clinically benign. In view of the high operative mortality, it is doubtful whether they should be removed in those cases in which ligation of the carotid arteries is necessary.—*Auth. Summ.*

MacComb, William S. [Memorial Hosp., New York City]: Carotid body tumors. *Ann. Surg.* 127: 269-277, Feb., 1948.—In a review of 10 surgically treated carotid-body tumors, the high postoperative mortality associated with the not infrequent necessity of ligating the common and internal carotid arteries during resection is emphasized. 4 deaths occurred in the 7 cases so ligated, due either to immediate cerebral anemia because of inadequate collateral cerebral circulation or to an ascending thrombosis in the internal carotid artery. The latter, it is presumed, originated in a ligature injury to the intima and might be guarded against by ligating over wide

fascial strips and the immediate use of anticoagulants. The Matas and other occlusion tests of the common carotid artery, when positive, are undoubtedly of value as indicators of the adequacy of the collateral cerebral circulation. Aspiration biopsy has been found to be both dependable and safe when representative samples of the tumor are obtained. Primary symptoms were the presence of a neck or pharyngeal mass, a Horner's syndrome, and vocal cord paralysis. There was no history of syncope in this series. 50% of the tumors were malignant and one of these was primarily bilateral. Case histories, a brief review of the literature, and the physiological and embryological background of these tumors are included.—*S. L. Perzik, M.D.*

Peterson, L. W. [Univ. Ill. Coll. Med., Chicago]: Minor surgery of the neck. *S. Clin. North America* 28: 56-68, Feb., 1948.

Rucker, William H. [Minneapolis, Minn.]: Congenital cysts and fistulas of the neck: with case reports. *Minnesota Med.* 31: 413-417, Apr., 1948.

THORACIC CAVITY

Brea, Mario M., & Imaz, Osvaldo Mazzini: Quiste pericardio-celómico. [Pericardio-celomic cyst.] *Bol. y trab., Acad. argent. de cir.* 31 (25): 845-850, 1947.—Case report.

Brohée, G. [Centre Gastro-Enterol. Brussels, Belg.]: Appendicite purulente et kyste sous-séreux intrathoracique du diaphragme. [Purulent appendicitis and subserous, intrathoracic cyst of the diaphragm.] *Acta gastro-enterol. belg.* 10: 455-457, Oct., 1947.—Dermoid cyst.

Brown, Robert B. [U. S. Navy]: Bronchiogenic cysts of the mediastinum. Report of a case. *U. S. Nav. M. Bull.* 48: 107-112, Jan./Feb., 1948.

Cooper, George, Jr.: Archer, Vincent W., & Mapp, John R. [Univ. Va. Hosp., Charlottesville]: Mesothelial mediastinal cysts ("pericardial cysts"). Differential diagnosis of shadows continuous with the anterior inferior mediastinum. *South. M. J.* 41: 285-295, Apr., 1948.

Davidson, Louis R., & Brown, Lowell [New York City]: Gastrogenous mediastinal cyst. *J. Thoracic Surg.* 16: 458-467, Oct., 1947.—Case report and review of literature.

La Tona, Joseph H., & Coleman, Francis C. [Mercy Hosp., Des Moines, Iowa]: Congenital gastro-enteric cysts of the thorax: A review and report of a case. *J. Iowa State M. Soc.* 38: 11-13, Jan., 1948.

Lindquist, Nils, & Wulff, Helge B. [Lund, Sweden]: Mediastinal enterocystoma. Report of a case in a seven-month-old child with impending suffocation, operation, and recovery. *J. Thoracic Surg.* 16: 468-476, Oct., 1947.

Perrin, M. B. [Winnipeg Gen. Hosp., Man.]: Mediastinal tumors. *Manitoba M. Rev.* 28: 149, Mar., 1948.—Report of 3 cases: ganglio-neuroma, lipoma, and 1 as yet undiagnosed.

Smart, Joseph [London Chest Hosp., Eng.]: A case of a large thymic cyst successfully removed from the anterior mediastinum. *Brit. J. Tuberc.* 41: 84-88, Oct., 1947.

ABDOMINAL CAVITY

Greene, Laurence F. [Mayo Clin., Rochester, Minn.]: Extreme renal displacement due to retroperitoneal tumors. *J. Urol.* 59: 174-178, Feb., 1948.—Report of 3 cases: lipoma, cyst of primitive urogenital-ridge origin, and cyst of adrenal gland.

Hickey, B. B. [Mosul, Iraq]: A dermoid cyst of the lesser omentum. *M. Press* 219: 19-20, Jan. 7, 1948.

Hill, Wm. Harry, & Glenn, Wadley R. [Crawford W. Long Memorial Hosp., Atlanta, Ga.]: Multiple pelvic malignancies. *South. Surgeon* 14: 192-194, Mar., 1948.—Case report: simultaneous bilateral ovarian cystadenocarcinoma and carcinoma of the sigmoid.

BREAST

Abramson, William, & Warshawsky, H. [U. S. Veterans Hosp., Dayton, Ohio]: Cancer of the breast in the male, secondary to estrogenic administration. Report of a case. *J. Urol.* 59: 76-82, Jan., 1948.—A case of cancer of the breast in a male who was undergoing estrogenic treatment for carcinoma of the prostate is presented. There is strong evidence that there is a causal relationship between the hormonal therapy and the development of cancer of the breast. The total amount of diethylstilbestrol used was 1997 mg. This treatment had extended over 489 days. Awareness of the likelihood of the development of cancer of the breast in the male receiving estrogenic therapy for carcinoma of the prostate is important. The breast changes incident to such therapy should be carefully observed clinically.—*Auth. Summ.*

Andreasen, A. T. [Calcutta, India]: Medullary carcinoma in an axillary breast. *Brit. J. Surg.* 35: 322-323, Jan., 1948.—Case report.

Bartlett, Edwin I. [San Francisco, Calif.]: Papilloma of the breast. *West J. Surg.* 56: 12-15, Jan., 1948.

Burns, C. W. [Winnipeg Gen. Hosp., Man.]: Tumour of the liver. *Manitoba M. Rev.* 28: 148-149, Mar., 1948.—Solitary metastasis of carcinoma of the breast.

Clarke, James C. [McNeal Memorial Hosp., Berwyn, Ill.]: Giant intracanalicular fibroadenoma of the breast. Report of a case. *Ann. Surg.* 127: 372-376, Feb., 1948.

Colin, L. Clarence [Baltimore, Md.]: Ten-year cures in carcinoma of the female breast. *South. M. J.* 41: 376-378, Apr., 1948.

Cutler, Max [Chicago, Ill.]: Cancer of the breast. *Kentucky M. J.* 46: 135-136, Apr., 1948.

Fernández, Orlando López [Havana, Cuba]: Cáncer de la mama en el hombre. Estudio basado en la revisión de once casos. [Cancer of the breast in the male. Study based on 11 cases.] *Arch. cubanos cancerol.* 6: 262-265, July/Sept., 1947.

Gordon-Taylor, Gordon: On cancer of the breast. *Ann. Roy. Coll. Surgeons England.* 2: 60-68, Feb., 1948.

Halpert, Béla, & Young, Millington O. [Sch. Med. Univ. Okla., Oklahoma City]: Carcinosarcoma of the mammary gland. *Surgery* 23: 289-292, Feb., 1948.—Case report.

Jackson, Arnold S. [Jackson Clin., Madison, Wis.]: Carcinoma of the breast in the absence of clinical breast findings. *Ann. Surg.* 127: 177-179, Jan., 1948.—Report of 3 cases.

Llewellyn, Henry Davies [Llanelly Gen. Hosp., Wales]: A giant adenocarcinoma of the breast. *Brit. J. Surg.* 35: 214-215, Oct., 1947.—Case report.

Macdonald, Ian [Sch. Med., Univ. South. Calif., Los Angeles]: The bleeding nipple as a diagnostic and therapeutic problem. *California Med.* 68: 1-4, Jan., 1948.

McCarthy, William D. [Oakland, Calif.]: The diagnosis of early breast cancer. *California Med.* 68: 7-10, Jan., 1948.

McGraw, Arthur B. [Grosse Pointe, Mich.]: Radical mastectomy. Prognosis after survival for five years. *Arch. Surg.* 55: 292-303, Sept., 1947.

Massopust, Leo C. [Marquette Univ. Sch. Med., Milwaukee, Wis.]: Infrared photographic study of the superficial veins of the thorax in relation to breast tumors. A preliminary report. *Surg., Gynec. & Obst.* 86: 54-58, Jan., 1948.—Infrared photography has been used to study the superficial venous patterns that may be altered by any condition affecting the circulation. 100 patients with breast complaints entering a dispensary from a cancer detection clinic were studied with the purpose of ascertaining if: (1) the pattern of the superficial veins of the thorax would be altered or disturbed by a tumor within the breast, (2) the tumor were malignant or benign, and (3) infrared photography might be of practical assistance in the diagnosis of cancer. Two normal venous patterns are found in the human female chest: the longitudinal, which radiates downward and laterally into the breasts from the area of the manubrial notch, and the transverse, which radiates laterally in both breasts from the pectoral venous plexus. 65 tumors were found among the 100 cases. 12 are described and the infrared photograph, "phlebogram," of each presented.

7 cases with malignant disease of the breast showed alterations in the venous pattern. 5 cases showed no alterations; 2 of these had normal breasts and 3 had benign pathological processes.

The author states that in some cases phlebograms revealed information difficult or impossible to obtain by other means and that in at least 6 cases in which the interpretation of the phlebogram was in disagreement with the clinical diagnosis, the subsequent pathological diagnosis confirmed the findings suggested by the photograph. He concludes that: "Further study of many more benign and malignant tumors might indicate that the infrared phlebogram may serve as an additional adjunct in the detection and classification of tumors of the breast."—*S. A. Wilkins, Jr., M.D.*

Meland, Orville N. [Los Angeles Tumor Inst., Calif.]: Carcinoma of the breast. *Ann. West. Med. & Surg.* 2: 121-123, Mar., 1948.

Neil, James M. [Oakland, Calif.]: Painful breast. *California Med.* 68: 5-6, Jan., 1948.

Oberhelman, Harry A. [Loyola Univ. Sch. Med., Chicago, Ill.]: Benign lesions of the breast. *S. Clin. North America* 28: 95-112, Feb., 1948.

Pavlovsky, Alejandro J., & Bertodano, Isidoro M. Cáceres: Mústitis quística y cáncer de mama. [Cystic mastitis and cancer of the breast.] *Bol. y trab., Acad. argent. de cir.* 31 (27): 909-924, 1947.

Perry, Thomas, Jr. [Rhode Island Hosp., Providence]: Adenocarcinoma of the breast. Report of a case recurring 27 years after radical mastectomy. *Rhode Island M. J.* 31: 44; 46, Jan., 1948.

Pullinger, B. D. [London, Eng.]: Cystic disease of the breast: Human and experimental. *Lancet* 2: 567-572, Oct. 18, 1947.—Human and experimental cystic disease of the breast are comparable. Discrepancies exist in the interpretation of the way cysts develop. Both conditions are probably brought about by excess of estrogen acting on mammary epithelium that responds atypically. The decisive factor is not merely excess or imbalance of estrogen but the nature of the parenchyma. Cystic disease of the breast is an entity independent of mammary cancer. It does not predispose to mammary cancer of mice when the cancer is activated by the tumor agent. Its relationship to chemical carcinogens remains to be determined.—*Auth. Summ.*

Schiuz, H. R., & Botsztejn, Ch. [Univ. Zürich, Swt.]: Die Abhängigkeit der Prognose der Mamma-Carcinome vom Tumorstadium und vom Lebensalter anhand von 702 Fällen. [Dependence of prognosis in breast carcinoma on the stage of the tumor and on the patient's age on the basis of 702 cases.] *Acta radiol.* 28: 611-622, Nov., 1947.

Sugarbaker, Everett D., & Wiley, Horace M. [Jefferson City, Mo.]: Carcinoma of the breast. Its present status. *J. Missouri State M. A.* 45: 1-22, Jan., 1948.—A review.

Trueman, K. R. [Winnipeg. Gen. Hosp., Man.]: Five-year survival in carcinoma of the breast. *Manitoba M. Rev.* 28: 149, Mar., 1948.

TREATMENT

Coller, F. A. [Ann Arbor, Mich.]: The diagnosis and treatment of breast tumors. The R. B. Sykes lecture. *J. Michigan State M. Soc.* 47: 399-400, Apr., 1948.—Lantern demonstration; abstract from Editor's notes.

Covington, E. Eugene [Mercy Hosp., Baltimore, Md.]: Cancer of the breast. The present status of irradiation. *Bull. Sch. Med. Univ. Maryland* 32: 150-158, Jan., 1948.

Davison, T. C., & Letton, A. H. [Atlanta, Ga.]: Testosterone in far advanced breast cancer. Preliminary report. *South. Surgeon* 14: 170-184, Mar., 1948.

Erskine, Arthur W. [Cedar Rapids, Iowa]: The management of advanced cancer of the breast. *Radiology* 50: 7-9, Jan., 1948.

Fitzwilliams, Duncan C. L. [St. Mary's Hosp., London, Eng.]: The treatment of early cancer of the breast. *M. Press* 219: 165-169, Feb. 25, 1948.

Goin, Lowell S. [Los Angeles, Calif.]: The place of radiation therapy in the management of breast cancer. *California Med.* 68: 11-13, Jan., 1948.

Gordon-Taylor, Gordon; McWhirter, R.; Cade, Stanford; Handley, R. S., & Allekin, F. M.: Discussion: the treatment of cancer of the breast. (Abridged) *Proc. Roy. Soc. Med.* 41: 118-132, Feb., 1948.

Harrington, Stuart W. [Mayo Clin., Rochester, Minn.]: Surgical treatment of carcinoma of the breast. *J. Michigan State M. Soc.* 47: 41-50, Jan., 1948.

Jones, Howard W., Jr. [Johns Hopkins Hosp. & Univ., Baltimore, Md.]: Testosterone in the treatment of advanced breast cancer. A preliminary report. *South. M. J.* 41: 4-11, Jan., 1948.—Fifteen advanced cases of carcinoma of the breast have been treated with injections of testosterone propionate, 300 mg. per wk. in divided doses. 3 of 5 cases with metastases to the bone had clinical and roentgenographic evidence of healing; another case had pain relief but steady progression of the lesion; one case was a complete failure. 2 of 10 cases of extrackeletal metastases showed startling improvement, while the remainder were failures. The variability of response noted in this and other series of breast carcinoma treated with testosterone is not at all understood and warrants further study.—*Auth. Summ.*

Klass, Alan [Winnipeg Gen. Hosp., Man.]: Testosterone propionate in the treatment of pulmonary metastases from breast carcinoma. (Report of a case.) *Canadian M. A. J.* 58: 56-58, Jan., 1948.

Lenz, Maurice [Presbyterian Hosp., New York City]: Tissue dosage in roentgentherapy of mammary cancer. *Acta radiol.* 28: 583-592, Nov., 1947.—A review of 162 patients receiving x-rays for breast cancer as pre- or post-operative, or as sole treatment, at the Presbyterian Hospital, 1923-1940, shows that tissue dosage influences the therapeutic result: less than 2000 r results in little growth restraint; viable cancer cells in mastectomy specimens are found even after a preoperative tumor dose of 4500 r. 10 nonoperated cancers clinically limited to the breast and axilla are free from clinical evidence of cancer for 7 to 10 yrs. after tumor doses of 6000-8000 r.—*Auth. Summ.*

Luin, J. J., van: De behandeling van mammacarcinoommetastases met testosteronpropionaat. [Treatment of mammary carcinoma metastases with testosterone propionate.] *Nederl. tijdschr. v. geneesk.* 91: 2834-2841, Oct. 4, 1947.—Includes case report.

Maisin, J. [Cancer Inst., Louvain, Belg.]: Le traitement du cancer du sein par eurietherapie et roentgentherapie. [Treatment of cancer of the breast by radium therapy and roentgen-ray therapy.] *Acta radiol.* 28: 593-610, Nov., 1947.

Maxwell, W. [Sydney, Australia]: After-care in radical amputation of the breast. *M. J. Australia* 1: 35-38, Jan. 10, 1948.

Moreno, Iván Goñi: Amputación mamaria bilateral. Apéxito cutáneo homólogo. Injertos "split-split." [Bilateral amputation of breasts; homologous apposition of skin. Split grafts.] *Bol. y trab., Acad. argent. de cir.* 31 (29): 998-1001, 1947.—Simultaneous bilateral amputation for cancer; case report.

Nathanson, Ira T. [Harvard M. Sch., Boston, Mass.]: Hormonal alteration of advanced cancer of the breast. *Bull. New England M. Center* 10: 1-6, Feb., 1948. Also in *S. Clin. North America* 27: 1144, Oct., 1947.

Neumann, Charles G., & Conway, Herbert [N. Y. Hosp., & Cornell Univ. M. Coll., New York City]: Evaluation of skin grafting in the technique of radical mastectomy in relation to function of the arm. *Surgery* 23: 584-590, Mar., 1948.—This report is based on an analysis of 389 patients on the surgical service of the New York Hospital from September 1, 1932, to December 31, 1940; 13 cases were excluded because of death which soon followed, or because of palliative surgery. Bilateral mastectomy was performed in 8 cases. Study was made of 384 case records of which 308 were sufficiently complete to analyze. Function was classified in 285 cases as: poor—less than 90-degree abduction; good—greater than 90 degrees but less than 160 degrees; excellent—greater than 160 degrees. Closure was classified in 287 cases: (1) without graft; (2) use of small graft (less than 60 sq. cm.); (3) use of large graft; (4) graft of unrecorded size. Of 308 patients, 95 were closed without graft; 23% had poor arm function.

With small grafts the functional result was poor in 19.5%. With large grafts 27% had unsatisfactory arm function. Only the cases with small grafts gave better functional results. The totals for this group show 19% with poor function—about the incidence of marked postoperative lymphedema: yet their analysis shows almost 12% with marked swelling; 45%, moderate; 45%, no swelling (still of this last number, 13.5% had poor function). In the group with marked edema, 35% had poor function. This latter figure may have been influenced by the application of x-rays, or the age of the patient, or the incidence of postoperative infection, prolonged drainage, or both. [Also, recurrent disease, not mentioned in this report, may have influenced unfavorably the results in the follow-up, especially the irradiated cases.] "Since x-ray therapy and closure of the wound without grafting both adversely affect the percentage of good functional results, it might be expected that their combined use would lead to the highest incidence of poor functional results. This is borne out by the analysis. 32% of patients whose wounds were closed with grafting, and who received x-ray therapy, had poor function of the arm, whereas only 15% of patients whose wounds were closed with graft, and who did not receive x-ray therapy, had poor results." [This statement seems of little value since the extent of disease and morbidity were not considered. What may be emphasized is that radical mastectomy followed by skin grafting has more chance of obliterating axillary dead space than primary closure. Hence the chances for prolonged serious drainage and subsequent infection are lessened. But may not immobilization of the arm when skin grafting is employed seriously impair arm function, especially in older age groups where periarticular fibrosis often results from immobilization? The use of skin graft alone does not insure the full preservation of arm function.]

One cannot help but call attention to an article from the same clinic (Holman, C.: McSwain, N., & Beal, J. J.: Swelling of the upper extremity following radical mastectomy. *Surgery* 15: 757-765, May, 1944) where in analyzing 100 similar cases the first statement in the authors' conclusion was: "Primary skin grafting has no influence on the occurrence of swelling of the arm following radical mastectomy."

The authors, evident disciples of the Halsted school in the surgical treatment of breast cancer, appear *pari passu* to prove the point of their method and still apologize when the swollen arm or poor function results. What the followers of this school either fail to realize, or are loath to admit, is that skin grafting as a part of radical mastectomy today is the survival of a fetish. Halsted's original operation was planned for far advanced breast cancers. Many had bulky primary lesions or extensive cutaneous involvement. Today, in the majority of instances, such a setting is unusual. If a patient with an extensive local condition is operated upon, one may question the advisability of radical surgery. On the other hand, with a primary lesion of 2 cm. or

under in the average breast, why should skin grafting be routinely employed? Does a small, well-localized cancer of the pylorus require total gastrectomy?—*N. E. Treves, M.D.*

Pickrell, Kenneth L.; Kelley, James W., & Marzoni, Francis A. [Duke Univ. Sch. Med., Durham, N. C.]: The surgical treatment of recurrent carcinoma of the breast and chest wall. *Plast. & Reconstruct. Surg.* 3: 156-172, Mar., 1948.—Few operations have been described for the extirpation of recurrent neoplastic lesions of the chest wall, even though approximately 1 patient out of every 3 upon whom a radical mastectomy has been performed will return with a local recurrence. Operative procedures have been designed and described for the extirpation of recurrent neoplastic lesions of the chest wall following radical mastectomy [4 case reports]. These operations are also applicable to primary tumors. Direct transfer-flap procedures utilizing superior, inferior, medial, and lateral pedicles have been demonstrated. 1 case is presented in which a double flap was used. A free skin graft was used successfully to cover the pericardium following resection of the chest wall.—*Auth. Concl.*

Reynolds, Eric [Oakland, Calif.]: Management of inoperable cancer of the breast. *California Med.* 68: 14-15, Jan., 1948.

Richards, G. E. [Toronto Gen. Hosp., & Univ. Toronto, Ont.]: Mammary cancer. The place of surgery and of radiotherapy in its management. Part I. A study of some of the factors which determine success or failure in treatment. *Brit. J. Radiol.* 21: 109-127, Mar., 1948.—A series of 1189 cases of mammary cancer treated by radical mastectomy plus postoperative x-rays yielded a 43% 5-yr.- and a 26% 10-yr.-survival rate. Using the Steintal classification, 81% 5-yr. survival was obtained in stage I; 43%, in stage II; and 13%, in stage III. The average 5-yr.-cure rate with surgery alone was 70% in stage I; 25-30% in stage II; and 5% in stage III. The author concludes that the increment in survival has been obtained by intensive postoperative x-ray therapy. A 22% 5-yr.-survival rate in untreated mammary cancer is cited.

Several factors influencing the prognosis are discussed. A more detailed classification of the clinical stage of the disease is suggested: 5 such stages with their criteria are given. The average growth rate of breast cancer is 1 cm. in diameter every 3 mos. If the growth rate is slower, the 5-yr.-survival averages 84%; when moderate, 63.5%; and it is 18%, when rapid growth occurs. Cancers in the outer hemisphere of the breasts yield 29% 5-yr. survival when nodes are involved; in the inner hemisphere, a 4% 5-yr.-survival rate. Grading of breast tumors is important but the over-all clinical setting is more significant. 5-yr. survival in a premenopausal group averaged 51%; in the menopausal group (concurrent with, and 5 yrs. after, the menopause), 40%; in the postmenopausal group, 40%. 6 of 24 cases occurring con-

currently with pregnancy survived 5 yrs. When pregnancy occurred subsequent to adequate control of breast cancer, a 55% 5-yr.-survival rate was noted in a group of 9 cases. Premenopausal cases subjected to x-ray castration gained 9% 5-yr.-survival rate over a comparable group in stages I and II not castrated. In a comparable group, radical mastectomy yielded 51% 5-yr. survival and 5% chest-wall recurrence; simple mastectomy gave 46% 5-yr. survival and 23% chest-wall recurrence, and local excision yielded 20% 5-yr.-survival rate and 44% local recurrence. A formula, "the clinical index of malignancy," weighing the above mentioned factors, is proposed as a means of prognosticating individual cases of breast cancer.

Vigorous preoperative x-rays eradicated mammary cancer in the breast in 25% of 82 cases; in 35% of those with axillary-node involvement; and in 50% of those with supraclavicular-node involvement. Preoperative x-rays do not interfere significantly with wound healing if the proper incision is used, the wounds closed without undue tension, and surgery instituted 6 wks. to 3 mos. after completion of therapy. Preoperative x-rays and radical mastectomy in a series of 70 cases yielded 100% 5-yr. survival in stage I; 50%, in stage II; and 45%, in stage III.

Stage-I cases are best treated by radical mastectomy and postoperative x-rays. A 5-yr.-survival rate between 75% and 90% is to be expected. Stage-II cases should be treated by preoperative x-rays and radical mastectomy and should yield a 5-yr.-survival rate of 65 to 70%. Stage-III cases are to be considered as radiological problems. With intensive x-rays, a few will become operable and the 5-yr.-survival rate should be between 35 and 43%. [Estimation of cancer destruction in regional nodes by x-rays is based upon clinical impression without pretreatment biopsy].—*J. A. Urban, M.D.*

Robinson, David W. [Univ. Kansas Hosps., Sch. Med., Kansas City]: Treatment of carcinoma of the breast. *Am. J. Surg.* 75: 484-488, Mar., 1948.—Of 324 patients with carcinoma of the breast operated on by 10 different surgeons, 91% were traced for 5 yrs. The operative mortality was 2.4% for the group. The term 5-yr. survival rather than cure is stressed. Of 85 patients in whom axillary nodes were not palpated clinically, 27 (31.8%) were found to have carcinoma in the nodes, whereas of 136 with clinically involved nodes, 36 did not have carcinoma, an error of 26.4%. The patients are classified according to the extent of the disease as follows: Group I, carcinoma confined to the breast; Group II, metastases to the axillary nodes only; Group III, metastases beyond the axilla; Group IV, hopeless cases. Although the addition of pre- or postoperative irradiation did not add to the 5-yr. survivals in the group as a whole, postoperative irradiation increased the 5-yr. survival in Group II by about 5%. 27 simple amputations were performed almost entirely for palliation, yet over 18% survived 5 yrs. Subradical amputations consisting of removal of the breast and axillary contents—leaving the pectoral muscles in place—were done in aged or debilitated

patients with low-grade malignant tumors. Of 20 patients (in Group I) so treated, 17 (85%) survived 5 yrs. as compared with 44 of 63 (70%) treated by radical mastectomy. In Group II, 18 of 74 (24.3%) lived 5 yrs. after radical operation as compared with 4 of 16 (25%) treated with the subradical procedure. The subradical operation would appear to have a place in the treatment of carefully selected patients.

The tumors were classified pathologically as: (1) scirrhous—fibrous stroma predominating; (2) medullary—epithelial elements predominating; (3) adeno- or ductal—definite adenomatous structure. The 5-yr. survival was identical for scirrhous and medullary (37%), whereas adeno- was 44%. The most common location of the primary tumor was the upper outer quadrant of the breast (52.6% of the total). The inner quadrant of the breast without axillary node involvement gave fairly high percentage (about 60%) of 5-yr. survivors, but the rate was definitely lower as compared with the outer quadrants when the axillary nodes were involved. Plastic closure was used almost routinely with the radical operation as opposed to skin grafting, which was seldom necessary. The local recurrence rate in Group I was 13.3%; in Group II, 20%; and in Group III, 44%. Including only Group I and II, the local recurrence rate was 16%. Of the 84 patients surviving 5 yrs., 25 or 29.8% died later of carcinoma. In Group I, 21.3% and in Group II, 50% of the 5-yr. survivors subsequently died of carcinoma. Of 22 10-yr. survivors, 9 have died or are living with cancer.—*M. W. Stearns, M.D.*

Kutishausser, Erwin [Kantonsspitals Genf., Switz.]: Beobachtungen an präoperativ bestrahlten Brustkrebsen. [Observations on preoperatively irradiated breast cancers.] Schweiz. Ztschr. f. Path. u. Bakt. 10 (Suppl.): 102-108, 1947.

Sacks, George [Groote Schuur Hosp., S. Africa]: A farewell to arm-pits? South African M. J. 22: 50-52, Jan. 24, 1948.—An argument for radical mastectomy versus simple mastectomy plus irradiation.—*D.A.S.*

Santy, Dargent, & Papillon [Lyon, France]: De l'action de la téléroentgenthérapie dans les cancers du sein et spécialement dans les formes inopérables. [The action of tele-röntgenotherapy in cancer of the breast, particularly the inoperable.] Presse méd. 55: 644-645, Oct. 1, 1947.

Stenstrom, K. W., & Baggenstoss, O. J. [Univ. Minn. & Univ. Hosps., Minneapolis]: Results of surgery and radiation for carcinoma of the breast with axillary metastasis. Acta radiol. 28: 623-632, Nov., 1947.—A survival study (up to Dec. 31, 1946) was made of all [110] patients with carcinoma of the breast treated between Jan. 1, 1927, and Dec. 31, 1941, who fulfilled the following criteria: A radical mastectomy had been performed at the University of Minnesota Hospital. Postoperative x-ray therapy had been started within 32

days after surgery. Satisfactory records were available to show that the pathologist had found metastases to axillary nodes. No distant metastases were definitely known to be present at the time of surgery. 45 patients (41%) survived 5 yrs. or more, and 12 (22%) 10 yrs. or more after operation. Representative statistics published by surgeons since 1936 have been selected to demonstrate results from radical mastectomy alone and with postoperative irradiation for patients with axillary metastasis. They show that postoperative x-ray therapy has consistently contributed to improved results.—*Auth. Summ.*

CARDIOVASCULAR SYSTEM

Andrews, George Clinton [Columbia Univ., Coll. Phys. & Surgeons, New York City]: A foolproof radium technic for treatment of hemangiomas. J. Invest. Dermat. 10: 95-97, Mar., 1948.

Carelli, Paul V., & Cangelosi, Joseph P. [Loyola Univ. Sch. Med.; St. Anne's Hosp., & St. Elizabeth's Hosp., Chicago, Ill.]: Angiosarcoma of the orbit. Am. J. Ophth. 31: 453-456, Apr., 1948.—Case report.

Dufresne, Origène [Montreal, Que.]: The treatment of angiomata. Canadian M. A. J. 58: 139-142, Feb., 1948.

Greenberg, Morris, & Angrist, Alfred [New York City]: Primary vascular tumors of the pericardium. A report of two cases. Am. Heart J. 35: 623-634, Apr., 1948.—Cavernous angioma and malignant angioendothelioma.

Jacobsson, Folke [Radiumhemmet, Stockholm, Sweden]: Two cases of cystic lymphangioma of the neck with mediastinal involvement. Acta radiol. 28: 705-714, Nov., 1947.

Junghagen, Sven [Centrallasarettet, Umca, Sweden]: Cases of haemangioma vertebrae roentgen treated with good results. Acta radiol. 28: 715-722, Nov., 1947.—Two cases of hemangioma vertebrae with grave neurological changes, which could be reduced by x-ray therapy, are described.—*Auth. Summ.*

Kaplan, I. W. [New Orleans, La.], & Toreson, Wilfred E. [Montreal, Que.]: Primary hemangioma of muscle. Am. J. Surg. 75: 614-617, Apr., 1948.

Kaulich, F. [Univ. Vienna, Austria]: Beitrag zum Vorkommen der sogenannten Glomustumoren. [Occurrence of so-called glomus tumors.] Monatschr. f. Ohrenh. 81: 576-579, Sept./Oct./Nov., 1947.—Case report of glomus tumor of the nose, typical except for rarity of location and its size.—*M.C.J.*

Laborde, Simone [Cancer Inst., Paris, France]: Le traitement des angiomes tubéreux des jeunes enfants. [Treatment of tuberous angiomas of young children.] Acta radiol. 28: 723-735, Nov., 1947.—When employed in too high doses in the treatment of tuberous angiomas in small children, radium and x-rays are re-

sponsible for various accidents: cutaneous lesions, inhibited growth of limbs, nervous accidents. The author proposes minimum doses either by means of flat enamelled containers allowing the use of β -rays, or by means of needles containing 1 or 2 mg. Ra (filtration: 0.5 mm. Pt) for the curie-puncture of voluminous angiomas. A series of photographs demonstrates the satisfactory esthetic results.—*Auth. Summ.*

Owens, Neal, & Stephenson, Kathryn L. [New Orleans, La.]: Hemangioma: an evaluation of treatment by injection and surgery. *Plast. & Reconstruct. Surg.* 3: 109-123, Mar., 1948.—Analysis of 95 cases.

Perlow, Samuel, & Roth, Harold A. [Michael Reese Hosp., Chicago, Ill.]: Glomus tumors. *Illinois M. J.* 93: 162-164, Mar., 1948.—Case report.

DIGESTIVE TRACT

Swenson, Paul C. [Philadelphia, Pa.]: Mass survey of the gastro-intestinal tract. *South. M. J.* 41: 108-112, Feb., 1948.—Of 2500 patients 50 or more yrs. old, examined by rapid fluoroscopic technique, 3 had early asymptomatic cancer, 5 warranted surgical exploration on suspicion of carcinoma.—*M. C. J.*

ORAL CAVITY

Ackerman, Lauren V., [Ellis Fischel State Cancer Hosp., Columbia, Mo.]: Verrucous carcinoma of the oral cavity. *Surgery* 23: 670-678, Apr., 1948.—During 7 yrs. 31 patients were observed with a variety of squamous carcinoma of the oral cavity designated as verrucous carcinoma. This lesion is delimited from other epidermoid carcinomas by typical clinical course, characteristic gross and microscopic findings, and excellent prognosis. The patients' av. age was 67 yrs.; 26 were men; 5, women. 18 had lesions of the buccal mucosa, of whom 11 were inveterate tobacco chewers. Growth was slow with local invasion and ulceration, occasional invasion or partial destruction of mandible, with infection and secondarily enlarged tender nodes, but local true lymph-node metastases were rare and distant metastases did not occur. The tumor may be soft and papillary but with coexisting infection becomes indurated. On resection, leukoplakia may be associated, and the lesion is invariably piled up in rugal folds with intervening deep clefts. Microscopically, surface piling up of keratin is followed by downward pushing club-shaped fingers of hyperplastic epithelium, with intact basement membrane, and later cystic degeneration of the central portions of the fingers. Superficial biopsies are often confusing, and even with the recommended thin, deep biopsies, the intact basement membrane and considerable differentiation may render diagnosis difficult.

Seven patients with superficial lesions were treated by radiation alone. One had recurrence after 42 mos.; others are still living or died of pneumonia. 7 patients were irradiated, with re-

currence necessitating later resection. None have died of the disease. 9 had local excision only, with 1 local recurrence. 11 had mandibular resections, 3 after recurrence following irradiation. X-ray examination revealed mandibular invasion when present (4 of 11); when absent, marginal erosion resulted from pressure and inflammatory attachment to periosteum; 1 wrong diagnosis occurred when destructive changes in mandible were a combination of radiation necrosis plus infection. There was 1 local recurrence after mandibular resection. Irradiation is apparently successful in relatively small superficial lesions, but chances of recurrence increase with the size of the tumor. Radical resection seems to be the treatment of choice in extensive lesions, with mandibular resection and upper neck dissection when fixation or invasion of bone is present.—*A. G. Foraker, M.D.*

Anon. [N. Y. Inst. Clin. Oral Path., New York City]: Carcinoma of the tongue. *New York State Dent. J.* 14: 39-40, Jan., 1948.—Case report.

Balyeat, Fred [Los Angeles, Calif.]: Cysts and fistulas of the branchial and thyroglossal ducts. *J. Oral Surg.* 6: 60-64, Jan., 1948.—A review.

Beckstrand, Grant [Seaside Memorial Hosp., Long Beach, Calif.]: Palliative procedures in advanced cancer of the mouth. *Radiology* 50: 10-18, Jan., 1948.

Binkley, J. Samuel [Los Angeles Tumor Inst., Calif.]: Cancer of the mouth. *Ann. West. Med. & Surg.* 2: 127-128, Mar. 1948.

Bodner, Hyman, & Bodner, B. Norton [Brooklyn, N. Y.]: Radicular cementoma. Report of a case. *Am. J. Orthodontics* 33: 842-846, Dec., 1947.

Brown, James Barrett, & McDowell, Frank [St. Louis, Mo.]: Neck dissections in cancer of the oral cavity. *Kentucky M. J.* 46: 114-125, Apr., 1948.—Reprinted from *Surg., Gynec. & Obst.* 79: 115, 1944.

Carr, Malcolm Wallace [New York City]: Squamous cell carcinoma of the tongue as a sequel to leukoplakia. *J. Oral Surg.* 6: 78-80, Jan., 1948.—Case report.

Chynoweth, John L. [Newark, Ohio]: Compound, composite odontoma. Report of a case. *Am. J. Orthodontics* 33: 856-858, Dec., 1947.

Cipollaro, Anthony C., & Einhorn, Marcus B. [N. Y. Post-Grad. M. Sch. & Hosp., Columbia Univ., New York City]: Granular cell myoblastoma. Report of two cases. *Arch. Dermat. & Syph.* 56: 812-818, Dec., 1947.

Desmond, Andrew M. [St. James Hosp., Balham, Eng.]: A case of lipomatosis of the tongue. *Brit. J. Surg.* 35: 210, Oct., 1947.—Case report.

Figi, Frederick A. [Mayo Clin., Rochester, Minn.]: Hemangiomas of the mouth. *Ann. Otol., Rhin. & Laryng.* 56: 853-866, Dec., 1947.—The vari-

- ous forms of hemangiomas occurring about the lips and mouth are reviewed, and the treatment of these different lesions and of the phleboliths at times encountered in cavernous angiomas is discussed. In general, radiation is the treatment of choice for strawberry birthmarks and cavernous hemangiomas in infants and small children. In adults cavernous lesions are more effectively treated with electrocoagulation and injections of boiling water or chemical sclerosing agents. Well-circumscribed hemangiomas often are best excised. Plexiform or racemose hemangiomas usually require ligation of the afferent vessels in addition to the measures employed in treatment of cavernous hemangiomas.—*Auth. Summ.*
- Figi, Frederick A.** [Mayo Clin., Rochester, Minn.]: The treatment of hemangiomas of the head and neck. *Plast. & Reconstruct. Surg.* 3: 1-10, Jan., 1948.
- Hall, John W., & Friedman, Milton** [N. Y. Univ. Coll. Med., New York City]: Histologic changes in squamous-cell carcinoma of the mouth and oropharynx produced by fractionated external roentgen irradiation. *Radiology* 50: 318-350, Mar., 1948.—[Excellent photomicrographs illustrative of irradiation changes in epidermoid carcinoma. Nothing, however, which has not been abundantly illustrated and described before.]—*F. W. S.*
- Humphreys, H. F.** [Univ. Birmingham, Eng.]: A note concerning carcinoma of the gum. *Birmingham M. Rev.* 15: 224, Jan., 1948.
- Jolles, B.** [Gen. Hosp., Northampton, Eng.]: Some aspects of malignant disease of the mouth and its treatment. *Brit. Dent. J.* 84: 28-32, Jan. 16, 1948.
- LeJeune, Francis E., & Steele, Clarence H.** [Tulane Univ. La. Sch. Med., New Orleans, La.]: A review of the available literature of the pharynx and pharyngeal surgery for 1946. *Laryngoscope* 58: 1-32, Jan., 1948.
- Morrison, Lewis F.** [San Francisco, Calif.]: California Cancer Commission Studies. Chapters XIII and I-A. Cancer of the tonsil and pharynx. *California Med.* 68: 100-102, Feb., 1948.
- Morwitz, S. M.** [Mt. Sinai Hosp., Chicago, Ill.]: Lymphosarcoma of the tonsil in a three-year-old child. *Ann. Otol., Rhin. & Laryng.* 56: 892-897, Dec., 1947.
- Reiss, Herman L.; Friedman, Milton, & Ginzler, Arthur:** Malignant mucous cell adenoma. Surgery and radium. *New York State Dent. J.* 14: 171-172, Mar., 1948.—Case report.
- Seabrook, Dean B.** [Portland, Oreg.]: Resection of the mandible. *West. J. Surg.* 56: 166-174, Mar., 1948.—Report of 6 cases.
- Smith, James B.** [Geisinger Memorial Hosp., Danville, Pa.]: Cavernous hemangioma of the soft palate. *J. Oral Surg.* 6: 85-86, Jan., 1948.—Case report.
- Szűcs, S.** [Univ. Debrecen, Hungary]: Sublingual fibroma. *Am. J. Orthodontics* 33: 847-848, Dec., 1947.—Case report.
- Taylor, Ralph W., & Huebsch, Raymond F.** [U. S. Navy]: Surgical removal of an odontoma and impacted anterior teeth: report of a case. *U. S. Nav. M. Bull.* 48: 116-118, Jan./Feb., 1948.
- Thoma, Kurt H.** [Mass. Gen. Hosp., & Harvard Univ., Boston]: **Holland, Daniel J., Jr.; Woodbury, Howard W.; Burrow, Jarrel G., & Sleeper, Edward L.:** Contribution to the oncology of the jaws. *Oral Surg., Oral Med. & Oral Path.* 1: 40-66, Jan., 1948.—Case reports: enostosis of the mandible; central giant-cell tumor of the mandible; recurrent adamantinoblastoma of the mandible; hemangioma of the cheek with phlebolithiasis; malignant lymphoma of the gingiva; fibrosarcoma of the capsule of the mandibular joint.—*M. C. J.*
- Thoma, Kurt H.** [Mass. Gen. Hosp., & Harvard Univ., Boston]: **Holland, Daniel J., Jr.; Woodbury, Howard W.; Burrow, Jarrel G., & Sleeper, Edward L.:** Oral conditions with a background of systemic disease. *Oral Surg., Oral Med. & Oral Path.* 1: 8-16, Jan., 1948.—Case reports of giant-cell tumor of maxilla associated with hyperthyroidism.—*M. C. J.*
- Thoma, Kurt H.** [Mass. Gen. Hosp., & Harvard Univ., Boston], & **Sleeper, Edward L.:** Gelatin sponge in the obliteration of cavities resulting from the excision of cysts and tumors of the jaws. *Oral Surg., Oral Med. & Oral Path.* 1: 24-39, Jan., 1948.
- Woodbury, Howard W.** [Mass. Gen. Hosp., Boston]: Diagnosis of oral epidermoid carcinoma. *Oral Surg., Oral Med. & Oral Path.* 1: 67-75, Jan., 1948.

SALIVARY GLANDS

- Cheyne, Virgil D.; Tiecke, Richard W., & Horne, Eleanor V.** [Iowa City]: A review of so-called mixed tumors of the salivary glands including an analysis of fifty additional cases. *Oral Surg., Oral Med. & Oral Path.* 1: 359-402, Apr., 1948.
- Furstenberg, A. C.** [Ann Arbor, Mich.]: Diseases of the salivary glands. *J.A.M.A.* 136: 1-4, Jan. 3, 1948.
- Heaton, T. G., & Shannon, E. H.** [Toronto, Ont.]: Mikulicz's disease. *Canadian M. A. J.* 58: 368-370, Apr., 1948.—Case report and survey of the literature.
- Hicken, N. Frederick; Stevenson, Vernon L., & Carlquist, John H.** [Univ. Utah M. Sch., Salt Lake City]: An unusually large myxosarcomatous tumor of the submaxillary gland. *Surgery* 23: 682-686, Apr., 1948.—Case report. The tumor measured 19.5 × 20 × 18 cm. and weighed 2450 gm.—*D. A. S.*
- Schulz, Milford D., & Weisberger, David** [Mass. Gen. Hosp., Boston]: Sialography: its value in

the diagnosis of swellings about the salivary glands. *Oral Surg., Oral Med. & Oral Path.* 1: 233-248, Mar. 1948.

ESOPHAGUS

Anon.: Carcinoma of the oesophagus and upper stomach. Professor Garlock's Address. *Lancet* 2: 631, Oct. 25, 1947.

DeBakey, Michael E., & Ochsner, Alton [Tulane Univ. La. Sch. Med., New Orleans, La.]: Carcinoma of the esophagus. *Postgrad. Med.* 3: 192-198, Mar., 1948.

Garlock, John H. [Columbia Univ., & Mt. Sinai Hosp., New York City]: Progress in the surgical treatment of carcinoma of the oesophagus and upper stomach. *Ann. Roy. Coll. Surgeons England* 2: 183-188, Apr., 1948; also in *Surgery* 23: 906-911, June, 1948.

Gauthier-Villars, P., & Dontzoff, A. [Paris, France]: Anatomie macroscopique du cancer de l'oesophage. (Étude des pièces chirurgicales.) [Macroscopic anatomy of cancer of the esophagus. (Study of surgical specimens.)] *Presse méd.* 55: 609-610, Sept. 20, 1947.

Leger, Lucien, & Tricard, Armand: Exérèse d'un cancer haut situé de l'oesophage thoracique avec rétablissement de la continuité. [Extirpation of a cancer situated high in the thoracic esophagus with re-establishment of continuity.] *Bull. méd., Paris* 62: 13-14; 17, Jan. 11, 1948.

Mikhelovich, M. S. [M. Inst., Archangel, Russia]: Polypi of the esophagus. *Am. Rev. Soviet Med.* 5: 105-106, Apr., 1948.—Case report of a pedunculated fibroma of the upper esophagus.

O'Connell, T. C. J. [St. Vincent's Hosp., Dublin, Eire]: Cancer of the oesophagus: modern treatment. *J. M. A. Eire* 22: 48-54, Apr., 1948.—Discussion and case report.

Simpson, Wyatt C. [Florence, Ala.]: Resection of the midthoracic esophagus for carcinoma. *J. M. A. State Alabama* 17: 221-226, Jan., 1948.—Two departures from previously reported techniques were utilized: (1) The distal esophagus is not removed until the posterior suture lines have been established. (2) No clamps are used on the end of the esophagus.—*Auth. Summ.*

Taquino, George J., & Joseph, Gerald F. [Sch. Med. La. State Univ., Baton Rouge, La.]: Carcinoma of the esophagus. An analysis of 145 cases with special reference to metastases and extensions. *Ann. Otol., Rhin. & Laryng.* 56: 1041-1058, Dec., 1947.—Earlier diagnosis in esophageal carcinoma demands alertness to the early symptoms. In lesions of the upper third there may be hoarseness alone; in lower sites, hiccup, substernal discomfort, and burning after meals; while carcinomas at the level of the diaphragm can give rise to an irritative cough. Barium swallow studies of the whole esophagus, and particularly esophagoscopy, are urged in the

presence of such symptoms. There are no contraindications to esophagoscopy by a trained operator; this is the only way that small nonobstructing esophageal cancers can be found. Without early diagnosis the chance of disease arrest is slim. Of 145 patients seen in 11 yrs. at the Charity Hospital and Hotel Dieu, New Orleans, only 19 were considered suitable for surgery. These were explored surgically and 11 resected, of whom 8 died postoperatively. 24 were irradiated. Only 2 surgical and 6 irradiated patients were benefited for as long as a year. Palliation by gastrostomy was carried out in 72; no figures on postoperative mortality and longevity are given.

In these 113 males, 32 females, the anatomical distribution was 13% in upper, 40% in middle, and 47% in lower third. Only 5 females had upper-third lesions in contrast to about 25% in Stockholm figures. There was a slight preponderance of Negro patients as compared with their over-all ratio in the Charity Hospital; they showed no greater delay in seeking aid than white patients. Symptoms lasted 1 to 18 mos. prior to hospitalization and were not correlated with the level of the obstructing cancer. The age range was 30 to 84 yrs.; 90% were more than 40. For no discernible reason, the aver. age was 5 yrs. younger in the cervical esophageal cancers. Pathological studies disclosed some evidence for the poor prognosis: (1) In the 124 with histological proof of cancer, there were 107 squamous and 17 adenocarcinomas. No grade I (Broders) cases were found in 41 of the former. (2) In the 44 autopsied patients, 4 had previously unsuspected esophageal primaries. (3) Metastases were widespread at operation or autopsy, especially to nodes along the full length of esophagus and stomach regardless of the primary level of individual cancers. Also instructive were 4 deaths by aortic rupture. The cancer permeation of vasa vasorum had apparently led to necrosis but not direct cancer invasion of the vessel wall. In most patients death was equally frequent from cachexia or secondary suppuration in mediastinum and lungs.—*J. L. Pool, M.D.*

Wilton, Jack [Johannesburg Hosp., S. Africa]: Total oesophagectomy for carcinoma of the middle third of the oesophagus. *South African M. J.* 21: 944-946, Dec. 27, 1947.

Wookey, Harold [Toronto, Ont.]: The surgical treatment of carcinoma of the hypopharynx and the oesophagus. *Brit. J. Surg.* 35: 249-266, Jan., 1948.—Discussion of the surgical treatment of carcinoma of the hypopharynx and esophagus with methods of esophageal reconstruction. Description of technique.—*D. A. S.*

STOMACH

Allen, Arthur W. [Mass. Gen. Hosp., Boston]: Cancer of the stomach. *Bull. New England M. Center* 10: 13-16, Feb., 1948.

Baravalle, Norberto: Tumores benignos del estómago. [Benign tumors of the stomach.] *An. de cir. [Argentina]* 12: 221-258, Sept., 1947.

- Barnes, William A. [Cornell Univ. M. Coll., New York City]: Unusual complications following resection of carcinoma of the cardiac end of the stomach. Report of a case. *Surgery* 23: 522-524, Mar., 1948.
- Barowsky, Harry [New York City]: Indications and contraindications for gastroscopy. *Am. J. Digest. Dis.* 15: 10-12, Jan., 1948.
- Baum, Lewis F.; Baum, Otto S., & Hermann, John H. [South Orange, N. J.]: *Thrombophlebitis migrans* in carcinoma of the stomach. *J. M. Soc. New Jersey* 45: 111-112, Mar., 1948.—Case report.
- Bell, H. Glenn [Univ. Calif. M. Sch., San Francisco]: The problem of gastric cancer in a university hospital. *Surgery* 23: 351-353, Mar. 1948.
- Bourne, W. A. [Roy. Sussex Co. & Hove Gen. Hosp., Eng.]: Cancer of the stomach in Addison's anaemia. *Brit. M. J.* 1: 92-94, Jan. 17, 1948.—Examination of 15 symptom-free pernicious-anemia patients revealed cancer in 3. Periodical x-ray and gastroscopic studies are strongly indicated in all cases of Addison's anemia in remission or relapse.—*Auth. Summ.*
- Byers, R. S., & Howard, John W. [Delaware Hosp., Wilmington]: Gastric neurilemoma [sic]. Report of four cases. *Delaware State M. J.* 20: 1-6, Jan., 1948.
- Campbell, James P.; Grimm, Harold A.; Andersen, Freeda, & Selmer, Erma [Wheaton, Ill.]: Experience with Papanicolaou stains in the study of gastric contents. *Rev. Gastroenterol.* 15: 21-32, Jan., 1948.
- Forty, Frank: Leiomyosarcoma of stomach. Thoracic-abdominal gastrectomy. *Proc. Roy. Soc. Med.* 41: 100-101, Feb., 1948.—Case report.
- Graham, Ruth M.; Ulfelder, Howard, & Green, Thomas H. [Mass. Gen. Hosp., Boston]: The cytologic method as an aid in the diagnosis of gastric carcinoma. *Surg., Gynec. & Obst.* 86: 257-259, Mar., 1948.—The cytologic method has been applied to gastric aspiration in 50 patients with gastric symptoms. Normal and malignant cells noted in gastric fluid are described. Of 24 patients proved to have carcinoma of the stomach, smears were positive in 15 instances. Of 7 patients with resectable lesions, smears were positive in 5; of 26 without cancer, the smear was reported positive in 1—a man with a benign gastric ulcer; 2 had extremely early malignant lesions, both detected by the cytologic technique.—*Auth. Summ.*
- Hartl, Hermann [Linz, Austria]: Zur Blindanastomose des Oesophagus mit dem Magen. [Anastomosis of esophagus and stomach.] *Krebsarzt* 3: 25-27, Jan., 1948.—Cardial and abdominal portions of esophagus were involved in the tumor. The esophagus was divided and implanted into the anterior wall of the stomach along a 3 cm. incision. There was no subsequent stenosis 10 mos. later.—*M. C. J.*
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SMALL INTESTINE

D'Albora, John B., & Ingegno, Alfred P. [Long Island Coll. Hosp., Brooklyn, N. Y.]: Carcinoid tumors of the small bowel. *Gastroenterology* 10: 310-326, Feb., 1948.—Report of 4 cases and review of the literature.

Sinclair, William, Jr. [Cleveland, Ohio]: Malignant carcinoid of the jejunum. *Ohio State M. J.* 44: 61-63, Jan., 1948.—A case of multiple (2) malignant carcinoids of the jejunum occurring in a 47-yr. old Negress which produced partial intestinal obstruction, intussusception, and metastases to the mesenteric lymph nodes and liver is reported.—*Auth. Summ.*

Tenner, Robert J. [Minneapolis, Minn.]: Lipomas of large and small intestine. A clinical and pathological study of twelve cases which produced symptoms necessitating surgical intervention. *Journal-Lancet* 68: 12-23, Jan., 1948.

COLON

Bacon, Harry E., & Broad, G. Gowing [Philadelphia, Pa.]: Pathogenesis of adenomatous polyps in relation to malignancy of large bowel. *Rev. Gastroenterol.* 15: 284-295, Apr., 1948.

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David, Vernon C. [Univ. Ill. Coll. Med., Chicago]: Life expectancy after radical removal of cancer of the large bowel based on pathological considerations. (Abstract) *Proc. Inst. Med. Chicago* 17: 41-42, Feb. 15, 1948.—Eighth in a series of lectures.

Dukes, Cuthbert E. [St. Mark's Hosp., London, Eng.]: Familial intestinal polyposis. *J. Clin. Path.* 1: 34-38, Nov., 1947.—The present knowledge of familial polyposis is discussed. A genealogical tree of 4 generations is presented: 1st generation: 1 male—death from cancer of rectum, aged 42 yrs.; 2d generation: 2 males, 4 females—death from cancer of rectum, aged 42, 52, 54, 39, 27, and 44 yrs., respectively; 1 male, 1 female, and 2 of undisclosed sex—uninvolved; 3d generation: 1 male—polypi at 44 yrs., carcinoma of splenic flexure at 56, carcinoma of rectum at 59, and carcinoma in colostomy at 60 yrs.; 1 female—polypi at 37 yrs.; 1 female—polypi at 11, colostomy for polyposis at 31, death from cancer of rectum at 52 yrs.; 1 female—death from cancer of colon at 33 yrs.; 1 male, 1 female and 2 of undisclosed sex—uninvolved; 4th generation: [5 males—apparently uninvolved to date, no ages given]. The author speculates as to whether familial polyposis may result from the chance mating of 2 individuals, each of whom was destined to die of cancer of the intestine. In 2 of the 10 families investigated at St. Mark's Hospital, the disease ap-

peared in a family in which both father and mother had died of cancer of the rectum or colon. As far as could be ascertained, this was the starting point of the polyposis in these 2 families. Polyposis is not a familial disease which is likely to spread and become more prevalent; on the contrary, polyposis families tend to die out.—*D. A. S.*

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Forty, Frank [Redhill Co. Hosp., Edgware, Eng.]: Associated carcinoma of colon and rectum. Report of two cases. *Proc. Roy. Soc. Med.* 40: 872-874, Dec., 1947.

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Martin, John L. [Montgomery, Ala.]: Problem of carcinoma of the colon in the Southeast. *South. Surgeon* 14: 7-14, Jan., 1948.

Michans, Juan R., & Diez, Enrique D.: Fibroleiomioma del colon descendente. [Fibroleiomyoma of the descending colon.] *Bol. y trab., Acad. argent. de cir.* 31 (30): 1009-1018, 1947.—Case report.

Michel, Marshall L. [Tulane Univ. Sch. Med., New Orleans, La.]: The diagnosis and treatment of acute malignant obstruction of the large bowel. *New Orleans M. & S. J.* 100: 397-408, Mar., 1948.—Analysis of 55 cases.

Nicholas, Charles [Guy's Hosp., Eng.]: Carcinoid tumours of the appendix. *Practitioner* 160: 235-236, Mar., 1948.—Case report and survey of the literature.

Nigam, R., & Prizeman, Hallett [M. Coll., Lucknow, U. P., India]: A case of lymphosarcoma

- of the ileo-caecal region with special reference to the technic of one stage right hemicolectomy. *Indian J. Surg.* 9: 164-166, Sept., 1947.
- Raven, Ronald W.: Partial hepatectomy and right hemicolectomy for carcinoma of the hepatic flexure of the colon. *Proc. Roy. Soc. Med.* 40: 876, Dec., 1947.—In extenso: *Brit. M. J.* 2: 249, 1947.
- Reichman, H. R. [Univ. Utah Sch. Med., Salt Lake City]: Multiple malignant lesions of the colon. *Am. J. Surg.* 75: 275-277, Feb., 1948.—Case report.
- Rosser, Curtice [Dallas, Tex.]: Management of surgical lesions of the left colon. *J. Internat. Coll. Surgeons* 11: 17-23, Jan./Feb., 1948.
- Ryan, D. Clark [Perth Children's Hosp., Australia]: A case of leiomyoma of the transverse colon causing obstruction in a child. *M. J. Australia* 1: 267-268, Feb. 28, 1948.
- Sanders, L. Carl [Memphis, Tenn.]: The early diagnosis of carcinoma of the colon and rectum. *Rev. Gastroenterol.* 15: 193-207, Mar., 1948.
- Schlicke, Carl P. [Spokane, Wash.]: Polyps of the large intestine. *Northwest Med.* 47: 276-278, Apr., 1948.
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- Wilensky, Abraham O. [New York City]: Carcinoma of the large intestine. A review of personal experience in private practice. *Rev. Gastroenterol.* 15: 55-86, Jan., 1948.
- Wilensky, Abraham O. [New York City]: Personal experiences with carcinoma of the right half of the colon in private practice. *M. Rec.* 161: 161-165, Mar., 1948.
- Winkler, H. [Allg. Krankenhaus, Vienna, Austria]: Beitrag zur Wiederherstellung der Kontinenz nach Operation wegen Mastdarmkrebs. [Restoration of continence after operation for cancer of the colon.] *Krebsarzt* 3: 81-86, Mar., 1948.—Technique of suturing to prevent fistulas after resection of the colon with preservation of the anus.—*M. C. J.*

RECTUM AND ANUS

- Bacon, Harry E., & Smith, Caleb H. [Temple Univ. M. Sch. & Hosp., Philadelphia, Pa.]: The arterial supply of the distal colon pertinent to abdominoperineal proctosigmoidectomy, with preservation of the sphincter mechanism. *Ann. Surg.* 127: 28-33, Jan., 1948.
- Best, R. Russell [Univ. Nebr. Coll. Med., Omaha]: Selection of operative procedure to avoid colostomy in carcinoma of rectum and rectosigmoid. *Surg., Gynec. & Obst.* 66: 98-106, Jan., 1948.—The authors are of the opinion that radical cancer surgery can be performed without removal of the sphincter mechanism. 11 cases are reported in which resection was performed and abdominal colostomy avoided by anastomosis. 3 types of sphincter-preserving anastomoses were used and are described.—*C. J. Miller, Jr., M.D.*
- Binkley, George E., & Sunderland, Douglas A. [New York City]: Diagnosis and treatment of papillary adenomas of the rectum. *Am. J. Surg.* 75: 365-368, Feb., 1948.
- Brust, John C. M. [Syracuse Univ. M. Center Hosps., N. Y.]: Extrarectal and extrasigmoidal masses. Proctosigmoidoscopic interpretation and evaluation. *Am. J. Surg.* 75: 380-383, Feb., 1948.
- Canónico, Abel N.: Cáncer recto-sigmoideo y de la porción distal del sigmoideo.—Resección y enteroanastomosis primarin. [Cancer of the rectosigmoid and of the distal portion of the sigmoid. Resection and primary enteroanastomosis.] *Bol. y trab., Acad. argent. de cir.* 31 (24): 823-838, 1947.—Case report.
- Charles, J. D., & McCarty, Robert [Milwaukee, Wis.]: Leiomyoma within the substance of the sphincter. *Am. J. Surg.* 75: 290-291, Feb., 1948.—Case report.
- Colvert, James R., & Brown Charles H. [Henry Ford Hosp., Detroit, Mich.]: Rectal polyps: diagnosis, 5 year follow-up, and relation to carcinoma of the rectum. *Am. J. M. Sc.* 215: 24-32, Jan., 1948.—Of 289 rectal polyps occurring in 235 patients, 175 (in 167 patients) were biopsied: 123 benign; 36 "benign but with signs of malignancy" (mitotic figures, hyperchromatic nuclei, piling up of epithelium); 16 malignant. All but 3 of those biopsied were removed by fulguration. Of 117 cases with benign polyps removed, followed 5-11 yrs., 3 developed rectal carcinoma; of 14 cases with malignant polyps removed, 1 developed rectal carcinoma. 43 of 68 cases not biopsied or removed were followed 5-11 yrs.; 3 subsequently developed rectal carcinoma. Because the total incidence of carcinoma for the 5-yr. period is not significantly different in the group that had their polyps removed (8.4%) and in the group that did not, the authors conclude that carcinoma usually de-

- velops very early in rectal polyps or is present from the start. They also conclude that rectal polyps, when malignant, are usually of a low grade of malignancy. [The conclusions are invalid as stated, because no comparison can be made between the clinical course of a series of biopsied cases whose tumors were removed and a series of untreated cases, the nature of whose tumors are not established by biopsy. Furthermore, a biopsy of one portion of a polyp is no indication of the benignity of the remainder of its structure. No worthwhile analysis can be made on this basis.]—*D. A. S.*
- Dixon, Claude F. [Mayo Clin., Rochester, Minn.]: Carcinoma of the rectum and lower part of the sigmoid flexure. Present-day management. *J. Michigan State M. Soc.* 47: 172-176, Feb., 1948.
- Dixon, Claude F. [Mayo Clin., Rochester, Minn.]: Carcinoma of the rectum and rectosigmoid. *Arizona Med.* 5: 41-45, Mar., 1948.
- Gilchrist, R. K., & David, Vernon C. [Presbyterian Hosp., & Coll. Med. Univ. Ill., Chicago]: Prognosis in carcinoma of the bowel. *Surg., Gynec. & Obst.* 86: 359-371, Mar., 1948.
- Green, W. W. [Toledo, Ohio]: Evaluation of the roentgenologic diagnosis of lesions of the rectum and sigmoid. *Am. J. Surg.* 75: 348-357, Feb., 1948.
- Grier, James P.; Nesselrod, J. Peerman, & Garner, Jay M. [Chicago, Ill.]: Carcinoma of the rectum. *Proc. Inst. Med. Chicago* 17: 69-70, Mar., 15, 1948.
- Jones, Thomas E.; Robinson, John R., & Meads, Garner B. [Cleveland Clin. Hosp., Ohio]: One hundred and thirty-seven consecutive combined abdominoperineal resections without mortality. *Arch. Surg.* 56: 109-116, Jan., 1948.
- Kaikini, V. M. [K. E. M. Hosp., Bombay, India]: Excision of the rectum with restoration of continuity. *Indian J. Surg.* 9: 133-136, Sept., 1947.—Report of 4 cases and discussion of technique.
- Landivar, Adolfo F.: Cáncer rectosigmoideo y de la porción distal del sigmoideo: resección y enteroanastomosis primarias. [Cancer of the rectosigmoid and of the distal portion of the sigmoid: resection and primary enteroanastomosis.] *Bol. y trab., Acad. argent. de cir.* 31 (25): 860-861, 1947.—Case report.
- Lloyd-Davies, O. V.: Carcinoma of the rectum with a single secondary in the liver. Synchronous combined excision and left hepatectomy. *Proc. Roy. Soc. Med.* 40: 875-876, Dec., 1947.
- McCrea, Lowrain E. [Philadelphia, Pa.]: Management of vesical dysfunction following abdominoperineal proctosigmoidectomy. *J. Internat. Coll. Surgeons* 10: 629-638, Nov./Dec., 1947.—In a group of 505 cases of malignant tumors of the bowel, the author considers trauma to the bladder and rectal nerves as the basic cause of bladder dysfunction complicating 13 of 292 abdominoperineal proctosigmoidectomies. This "paralytic vesical atony" was shown by inability to urinate, with complete urinary retention and associated vesical distention. Persistent contraction of the internal sphincter, due to an apparent predominant sympathetic influence after removal of the inferior hypogastric or the pelvic plexus, is suggested as the *modus operandi*. [Although cystometric findings are presented, they are not conclusive of neurological damage.] A persistent residual of more than 60 cc. is an indication for reinsertion of the retention catheter. Syntropan, 200 mg. t.i.d., is recommended for its tone-decreasing effect on the smooth muscles of the internal vesical sphincter. The cystitis that occurs was benefited by the sulfathalidine administered routinely before this type of bowel surgery. Time and maintenance of a bladder at rest, without infection, are considered to be the greatest factors permitting restitution of normal vesical activity.—*C. J. Miller, Jr., M.D.*
- Manning, W. R. [Tucson, Ariz.]: Diagnosis and treatment of carcinoma of the rectum. *Arizona Med.* 5: 49-56, Mar., 1948.
- Moskowitz, Lester [New York City]: Malignant melanoma (melanosarcoma). *Am. J. Surg.* 75: 283-284, Feb., 1948.—Case report.
- Müller, Olle [King Gustaf V's Jubilee Clin., Lund, Sweden]: Anorectal malignant melanomas. A clinical study based on two cases. *Acta chir. Scandinav.* 96: 39-46, Sept. 10, 1947.
- Myers, Hu C.; Bush, A. Kyle, & Lea, Melvin [Philippi, W. Va.]: Carcinoma of the colon and rectum. *West Virginia M. J.* 44: 75-78, Apr., 1948.—Analysis of 34 cases.
- Nickel, William F. [New York City], & Chenoweth, Arthur I.: Resection of the rectum with preservation of the anal sphincter. *Surgery* 23: 480-491, Mar., 1948.—The operative technique for resection of the rectum with preservation of the anal sphincter, as performed by Hochenegg, and modified by the abdominoperineal approach by several American surgeons, is presented. The present study is a review of 68 patients, having a "pull through" operation performed on the Surgical Service of New York Hospital between September, 1932, and December, 1946. Approximately 15 different surgeons performed the operations. There was a postoperative mortality rate of 13.2%; all deaths occurred prior to 1941. A 5-yr.-survival rate of 40% and a 10-yr. rate of 26% is not encouraging for support of the operative procedure. The function of the external sphincter in 34 patients (in which an adequate follow-up was available) was considered perfect in 3; good, 7; fair, 10; and poor in 14. The authors concluded that the "pull through" operation is applicable only to lesions whose lower margin is at least 6 cm. above the anal orifice, and whose upper limit is at or below the peritoneal reflection. [No consideration was given to the size of

- the cancer or the rate of growth.]—C. J. Miller, Jr., M.D.
- Nigam, R. [King George's Hosp., Lucknow, India]: A case of dermoid arising from the rectal wall. *Brit. J. Surg.* 35: 218-219, Oct., 1947.
- Parsons, Willard H. [Vicksburg, Miss.]: Cancer of the rectum. (Editorial symposium.) *Mississippi Doctor* 25: 274-275, Jan., 1948.
- Pearse, H. E. [Taunton, Eng.]: Cryptic cancer of the anorectal region. *Brit. J. Surg.* 35: 327, Jan., 1948.—Case report: colloid carcinoma arising in anal fistula.
- Rankin, Fred W., & Johnston, Coleman C. [Lexington, Ky.]: Surgical treatment of cancer of the rectum and rectosigmoid. *J.A.M.A.* 136: 371-375, Feb. 7, 1948.—The rediscovery of the "pull-through operation" has in recent years created controversy as to the type of procedure most acceptable in the treatment of cancer of the rectum. Data are lacking in the literature on favorable end-results of such an attack. Radical extirpation is the method of choice and the Miles combined abdominoperineal resection of the rectum has yet to be improved. The presence or absence of node involvement is the best prognostic yard-stick; longevity is in direct proportion to this. The histological grade of the growth is in direct proportion to node involvement; the higher the grade, the earlier extension will take place. A review of 336 patients with cancer of the rectum and rectosigmoid seen by the authors in a 7-yr. period before 1941 is presented: 310 operated upon; 233 resected, a resectability rate of 75.1%. In 167 (71.7%), the Miles operation was found applicable. 45% showed node metastases; 25% of these lived 5 yrs. or longer. In the 55% without node metastases, 43.8% survived the 5-yr. period. In the 167 patients having the Miles resection, there was a mortality of 5.3%.—C. J. Miller, Jr., M.D.
- Raven, Ronald W. [Roy. Cancer Hosp. (Free), Eng.]: Radical excision of the rectum without colostomy. *M. World* 68: 77-80, Mar. 12, 1948.
- Schofield, James D. [Philadelphia, Pa.]: Ischioanal dermoid. *Am. J. Surg.* 75: 278, Feb., 1948.—Case report.
- Skir, Isaac [Brooklyn Hosp., N. Y.]: Mucinous carcinoma associated with fistulas of long-standing. *Am. J. Surg.* 75: 285-289, Feb., 1948.—Report of 3 cases.
- Smith, Daugh W. [Nashville, Tenn.]: Malignant lesions of the rectum, rectosigmoid, and sigmoid. *J. Tennessee State M. A.* 41: 119-127, Apr., 1948.—Survey of 105 cases.
- Swinton, Neil W. [Boston, Mass.]: Diagnosis and treatment of mucosal polyps of the rectum and colon, with early malignant change. *Am. J. Surg.* 75: 369-379, Feb., 1948.
- Thomas, Ralph A. [Veterans Adm. Hosp., Hines, Ill.]; Kline, Philip S., & Seed, Linton: Carcinoma of the rectum and rectosigmoid. A statistical analysis of eight hundred and forty-four cases. *Arch. Surg.* 56: 92-108, Jan., 1948.
- Turner, John [Melbourne, Australia]: Carcinoma of the rectum. *Australian & New Zealand J. Surg.* 17: 115-136, Oct., 1947.
- Wilensky, Abraham O. [New York City]: Personal experience with carcinoma of the rectosigmoid and rectum in private practice. *J. Internat. Coll. Surgeons* 11: 73-81, Jan./Feb., 1948.

LIVER AND BILIARY TRACT

- Benjamin, Edwin G. [Minneapolis, Minn.]: Malignancy of the gall bladder associated with chronic cholelithiasis. *Minnesota Med.* 31: 274-275, Mar., 1948.
- Brunschwig, Alexander [Memorial Hosp., New York City]: Cancer of the liver, bile ducts and pancreas. *J.A.M.A.* 136: 28-35, Jan. 3, 1948.—A discussion of symptomatology, diagnosis, treatment, and prognosis of primary and secondary malignant tumors of the liver, and cancer of the bile ducts, gallbladder, papilla of Vater, and pancreas.—D. A. S.
- Hunt, Henry F., & Berkheiser, Samuel W. [George F. Geisinger Memorial Hosp., Danville, Pa.]: Primary carcinoma of the liver. *Pennsylvania M. J.* 51: 755-758, Apr., 1948.—Report of 13 cases (0.36% in 1370 autopsies) and review of the literature.
- Lenzi, Sergio, & Milletti, Antonio [Univ. Bologna, Italy]: Sulla biopsia epatica aspiratoria. [Aspiration biopsy of the liver.] *Minerva med.* 2: 223-231, Sept. 15, 1947.—A review and brief discussion of 30 cases.
- Morley, John: Carcinoma of the ampulla of Vater. *Brit. J. Surg.* 35: 146-151, Oct., 1947.—Six cases of carcinoma of the ampulla of Vater treated by a radical two-stage operation with ligation of the pancreatic duct are recorded. The relative merits of the one- and the two-stage operation are discussed. One case of apparent spontaneous cure of an ampullary carcinoma is recorded.—*Auth. Summ.*
- Patton, Robert J. [Springfield, Ill.]: Hamartoma of the liver. *Ann. Surg.* 127: 180-186, Jan., 1948.—Case report.
- Sainburg, Frank P., & Garlock, John H. [Mt. Sinai Hosp., New York City]: Carcinoma of the gall bladder. *Surgery* 23: 201-205, Feb., 1948.—Of 75 patients with carcinoma of the gallbladder, 65 were operated upon, with only one survivor (13 yrs.) longer than 3 yrs. When this disease is diagnosed clinically it is virtually incurable, hence must be prevented. Overwhelming evidence points to gallstones as a predisposing factor in carcinoma of the gallbladder. Since the incidence of death due to

malignant transformation in calculous gall-bladders far exceeds the prevailing operative mortality of cholecystectomy, removal of even asymptomatic calculous gallbladders is indicated on these grounds alone.—*Auth. Summ.*

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Thompson, James H., & Bostick, Warren L. [Univ. Calif. M. Sch., San Francisco]: Primary spindle cell fibromyosarcoma of the gall-bladder. *California Med.* 68: 95-98, Feb., 1948.—Case report.

PANCREAS

Anderson, H. A. [Tacoma, Wash.]: Neoplasms of the pancreas. *Northwest Med.* 47: 106-108, Feb., 1948.—A review.

Baker, Joel W. [Mason Clin., Seattle, Wash.]: Problems involved in pancreatoduodenal resection. *West. J. Surg.* 56: 1-11, Jan., 1948.

Blain, Alexander W., & Jarrin, Nelson [Detroit, Mich.]: Resection of the head of the pancreas for carcinoma. *Alexander Blain Hosp. Bull.* 7: 29-37, Feb., 1948.—Reprinted from *J. Michigan State M. Soc.* 46: 1171, Oct., 1947.

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Jemerin, Edward E., & Samuels, Norman A. [New York City]: Cystadenoma of the pancreas. *Ann. Surg.* 127: 158-170, Jan., 1948.—Case report and review of literature.

Kiernan, Paul C. [Mayo Clin., Rochester, Minn.]: Surgical treatment of carcinoma of the head of the pancreas and of the thyroid. Report of a case. *M. Ann. District of Columbia* 17: 216-218; 255, Apr., 1948.

Mills, W. M., & Wakeman, Don C. [Topeka, Kans.]: Surgery of pancreatic cysts. *J. Kansas M. Soc.* 49: 57-60, Feb., 1948.—Case report.

Mullen, Bernard P. [Seattle, Wash.]: Surgery of the pancreas. *Northwest Med.* 47: 108-111, Feb., 1948.

Olsson, Olle [Univ. Clinics, Lund, Sweden]: Roentgen examination as an aid in the diagnosis of islet adenoma in the pancreas. *Acta radiol.* 28: 833-837, Nov., 1947.

Pessagno, Daniel J., & Schaefer, John F. [Univ. Md. Sch. Med., Baltimore]: Pancreatic cysts: with report of two cases. *South. M. J.* 41: 166-169, Feb., 1948.—A review of literature and report of 1 true and 1 pseudocyst.—*M. C. J.*

Saltzstein, Harry C., & Johnson, Walter S. [Harper Hosp., Detroit, Mich.]: Carcinoma of the pancreas: operative problems. *Gastroenterology* 10: 442-451, Mar., 1948.—Report of 3 cases of pancreatic cancer and 1 case of unexplained common bile-duct obstruction.

Whipple, Allen O. [New York City]: The early diagnosis of pancreatic and ampullary growths. An evaluation of their surgical treatment. *J. Michigan State M. Soc.* 47: 169-171, Feb., 1948.

Wirts, C. Wilmer, Jr. [Jefferson Hosp., Philadelphia, Pa.]: Report of a case of carcinoma of the tail of the pancreas. *Gastroenterology* 10: 327-331, Feb., 1948.

ENDOCRINE ORGANS

Beaumont, G. E. [Middlesex & Brompton Hosps., Eng.]: A parathyroid tumour. *M. World* 67: 807-809, Feb. 20, 1948.—Case report: adenoma with hyperparathyroidism.

Black, B. Marden [Mayo Clin., Rochester, Minn.]: Adenocarcinoma of parathyroid origin with hyperparathyroidism, local recurrence and metastases: report of case. *Proc. Staff Meet., Mayo Clin.* 23: 8-14, Jan. 7, 1948.

Davidoff, Leo M., & Feiring, Emanuel H. [Montefiore Hosp., New York City]: Surgical treatment of the tumors of the pituitary body. *Am. J. Surg.* 75: 99-136, Jan., 1948.

Grant, Francis C. [Philadelphia, Pa.]: Surgical experience with tumors of the pituitary gland. *J.A.M.A.* 136: 668-672, Mar. 6, 1948.—In treatment of chromophobic and eosinophilic pituitary-gland adenomas, combined surgical and irradiation therapy are more effective than surgical measures alone. The suprasellar congenital tumors, the craniopharyngiomas, have a poor prognostic outlook. They are not radiosensitive. Surgical reports show a high mortality, with few survivors for any length of time.—*Auth. Summ.*

Heller, Edward P. [Kansas City, Mo.]: Hyperparathyroidism. Summary of important findings in a ten year study of a case. *J. Missouri State M. A.* 45: 26-28, Jan., 1948.

McGovern, V. J. [Roy. Prince Alfred Hosp., Camperdown, Australia]: Phillips, G. E., & Wyke, B. D.: An undifferentiated pituitary adenoma of unusual size. Report of a case. *J. Neurosurg.* 5: 202-208, Mar., 1948.—The tumor capsule was incised at operation and all visible tumor tissue removed by suction and curettage. At autopsy 5 days later the remaining tumor tissue measured $6.5 \times 3.5 \times 3$ cm. and weighed 48 gm. Microscopic diagnosis: pregranulocytic adenoma.—*D. A. S.*

Twombly, Gray H., & Pack, George T., Ed.: *Endocrinology of Neoplastic Diseases. A Symposium by Eighteen Authors.* New York. Oxford Univ. Press. 1947. 392 pp. \$11.00.—This volume is a compilation of accumulated data, both clinical and experimental, on tumors of the organs of internal secretion. Consideration is also given to the endocrine factors of neoplasms of other organs, viz.: breast, uterus, prostate. Although there is adequate coverage of the entire subject, no new facts are presented in this symposium. The bibliography, which is extensive, makes this volume particularly valuable as a book of reference. The subjects and the contributing authors are:

Introduction, Gray H. Twombly, & George T. Pack.—I. Tumors in Experimental Animals Receiving Steroid Hormones, W. U. Gardner.—II. Experimental Investigations Concerning the Role of the Pituitary in Tumorigenesis, Hans Selye.—III. The Endocrine Effects of Pituitary Tumors, William J. German.—IV. Ovarian Tumors with Sex Hormone Function, Emil Novak.—V. Endocrine Factors in the Origin of Tumors of the Uterus, Howard C. Taylor, Jr.—VI. The Relationship of Hormones to Diseases of the Breast, Ira T. Nathanson.—VII. The Effect of Sex Hormones on Skeletal Metastases from Breast Cancer, Joseph H. Farrow.—VIII. Benign Hypertrophy and Carcinoma of the Prostate, Robert A. Moore.—IX. The Endocrine Treatment of Cancers of the Prostate Gland, Archie L. Dean, Helen Q. Woodard, & Gray H. Twombly.—X. The Relationship of Hormones to Testicular Tumors, Gray H. Twombly.—XI. Adrenal Cortical Tumors—Physiologic Considerations, Allan T. Kenyon.—XII. Hormonal Tumors of the Adrenal, George F. Cahill.—XIII. The Endocrine Activity of Thyroid Tumors and the Influence of the Thyroid Hormone on Tumors in General, Jacob Lerman.—XIV. The Endocrine Aspect of Enlargements of the Parathyroid Glands, Oliver Cope.—XV. Hyperinsulinism in Relation to Pancreatic Tumors, Allen O. Whipple.—XVI. The Endocrinologic Aspects of Tumors of the Pineal Gland, Leo M. Davidoff.—*H. E. E.*

Young, Millington O., & Halpert, Béla [Univ. Okla., Sch. Med., Oklahoma City]: Parathyroid adenoma with generalized metastatic calcification. *Arch. Path.* 44: 628-634, Dec., 1947.—Extensive metastatic calcification in a white man aged 49 with hyperparathyroidism was caused by an adenoma of the left inferior parathyroid gland, located in the posterior part of the superior mediastinum. The condition was

not diagnosed during life. Death was due to the sequel of thrombosis of a branch of the superior mesenteric artery caused by calcific change in its wall.—*Auth. Summ.*

ADRENAL

Bean, Lawrence Lytton, & Benson, Ralph Crielwell [M. C., U. S. Navy, & Univ. Calif. Hosp., San Francisco]: Tumors of the adrenal cortex. *Am. J. Surg.* 75: 589-596, Apr., 1948.—Report of 2 cases.

Blacklock, J. W. S.; Ferguson, F. W.; Mack, W. S.; Shafar, J., & Symington, T. [Roy. Infirmary, Glasgow, Scotland]: Phaeochromocytoma. *Brit. J. Surg.* 35: 179-197, Oct., 1947.—Report of 6 cases: with clinical and pathological data.—*J. M. Sether, M.D.*

Cerviño, J. M.; Manaro, J. Morató; Pollak, E., & Proto, A. [Inst. Endocrinology, Montevideo, Uruguay]: Síndrome de Cushing por tumor suprarrenal. Con alta eliminación de andrógenos y estrógenos y reacción positiva en el tumor con la fenilhidrazina. [Cushing's syndrome from suprarenal tumor. With abnormally high androgen and estrogen elimination and positive phenylhydrazine reaction in the tumor.] *Medicina, Buenos Aires* 7: 468-484, Oct., 1947.—A case of adrenal carcinoma, with complete atrophy of the opposite gland, had a prolonged evolution that gave a Cushing syndrome in which certain clinical symptoms and laboratory tests were unusual: hemorrhagic metropathy, diarrhea, a dermatosis of the keratosis rubra type, soft edema and hypertrophy of the clitoris, muscular atrophy and osteoporosis which appeared towards the end of the affection. The K level was at the highest normal. There was neutrophilia and marked lymphopenia, severe disturbances in the sugar metabolism and marked elimination of estrogens and ketosteroids in the urine. There was a positive phenylhydrazine reaction and birefringent crystals were observed in some regions of the tumor.—*Auth. Summ.*

Commons, Robert R., & Callaway, Claude P. [Boston City Hosp., Mass.]: Adenomas of the adrenal cortex. *Arch. Int. Med.* 81: 37-41, Jan., 1948.—Adrenal cortical adenomas larger than 3.0 mm. were present in 216 (2.86%) of 7437 consecutive autopsies. Vacuolated and eosinophilic cells with architecture different from that of normal adrenal cortex were present histologically. The incidence was equal in males and females and low in the first three decades of life with progressive increase in later age groups. With allowance for age groups, there was no significant difference in incidence of hypertensive cardiovascular disease, cardiac enlargement, diabetes mellitus, or gonadal changes in patients with adrenal cortical adenomas as compared with patients without such tumors.—*J. M. Sether, M.D.*

Holland, C. W. [Dalhousie Univ., Halifax, N. S.], & Strickland, S. C.: Adrenal medullary pheochromocytoma. *Canadian M. A. J.* 58: 330-

334, Apr., 1948.—Report of a case with successful surgical removal and of a case of extramedullary chromaffinoma.—*D. A. S.*

Lawrence, H. E., & Welch, C. Stuart [Joseph H. Pratt Diagnostic Hosp., Boston, Mass.]: Paroxysmal hypertension and pheochromocytoma: surgical removal of the tumor. Report of a case. *Bull. New England M. Center* 9: 231-237, Oct., 1947.

Patterson, Jocelyn [Charing Cross Hosp. M. Sch., Eng.]: Diagnosis of adrenal tumours. *Lancet* 2: 580-581, Oct. 18, 1947.—The new color reaction for dehydroisoandrosterone described demonstrates excess of this compound in extracts of urine from adrenal-tumor cases. Under comparable conditions urines from cases of adrenal hyperplasia are negative; hence the reaction differentiates cases of adrenal tumor from other adrenal cases with high 17-ketosteroid output. The same reaction is given by isoandrosterone, and by a third substance present with dehydroisoandrosterone in urine from cases of adrenal tumor. Neither of these additional compounds complicates the reaction in the diagnosis of adrenal tumors.—*Auth. Summ.*

Roth, Grace M., & Kvale, Walter F. [Rochester, Minn.]: Further studies with the histamine test for pheochromocytoma. *J. Lab. & Clin. Med.* 32: 1510, Dec., 1947.—Intravenous injection of 0.05 or 0.025 mg. of histamine base into 4 patients with pheochromocytoma produced the clinical syndrome, including hypertension and characteristic symptoms. After surgical removal of the tumor, no such reaction followed similar injection. In 1 patient with pheochromocytoma and persistent hypertension the test was negative. In 200 patients with hypertension and 50 with other clinical conditions, no untoward effects followed the test.—*D. A. S.*

Samuel, Eric [Johannesburg, S. Africa]: Calcification in suprarenal neoplasms. *Brit. J. Radiol.* 21: 139-142, Mar., 1948.—Case report and discussion.

Staffieri, Juan José; Cames, Oscar, & Cid, José M. [Rosario, Argentina]: Síndrome hipoglucémico como manifestación más destacada de un tumor córticosuprarrenal. [Hypoglycemic syndrome as a symptom of a suprarenal cortex tumor.] *Medicina, Buenos Aires* 7: 543-565, Dec., 1947.—A patient with the syndrome of hypoglycemia produced by a corticosuprarrenal tumor without the simultaneous presence of the characteristic manifestations of adrenal disturbances usual in this type of tumor is described. A review of the literature indicates this to be the first case of its kind. The diagnosis previous to the operation was a pancreatic tumor. Operation and anatomopathologic studies revealed the adrenal tumor [sarcomatous dysembryoplasia] and the etiology. Postoperative disappearance of a goiter, a gynecomastia, and a hepatosplenomegaly indicate a causal relation between the tumor and those alterations which the authors cannot explain definitely. It has not been possible to study the hormonal activity of the tu-

mor nor to determine estrogenic substances in the patient before or after the operation.—*From Auth. Summ.*

Weber, Eugene J., & Menten, Maud L. [Univ. Pittsburgh, & Children's Hosp., Pittsburgh, Pa.]: Histologic studies on a virilizing tumor of the adrenal cortex. *Am. J. Path.* 24: 293-303, Mar., 1948.—Study of a tumor in a 3½-yr.-old boy.

THYROID

Allende, Carlos L.: Metástasis "funcionante", escapular, de adenocarcinoma tiroideo; escapulectomía subtotal y tiroidectomía. [Encapsulated "functioning" metastasis of adenocarcinoma of the thyroid; subtotal capsulectomy and thyroidectomy.] *Bol. y trab., Acad. argent. de cir.* 31 (31): 1074-1077, 1947.—Case report.

Black, B. Marden [Mayo Clin., Rochester, Minn.]: Papillary adenocarcinoma of the thyroid gland, so-called lateral aberrant thyroid tumors. *West. J. Surg.* 56: 134-144, Mar., 1948.

McClintock, John C., & Klink, Gustavus H., Jr. [Albany M. Coll., N. Y.]: Neoplastic disease of the thyroid gland. *West. J. Surg.* 56: 52-57, Jan., 1948.

McSwain, Barton, & Diveley, Walter [Vanderbilt Univ. Sch. Med., Nashville, Tenn.]: Malignant tumors of the thyroid gland. *Surgery* 23: 525-541, Mar., 1948.—Report of 23 cases.

Piazzentini, Luigi [Univ. Bologna, Italy]: Tumori maligni in tiroidi laterali aberranti. [Malignant tumor in lateral aberrant thyroid.] *Arch. ital. chir.* 69 (6): 425-440, 1947.—Case report; carcinoma.

Ramsey, Frank B. [Indianapolis, Ind.]: Surgical aspects of carcinoma of the thyroid gland. *J. Indiana State M. A.* 41: 395-397, Apr., 1948.—Case report and discussion.

Rawson, Rulon W.; McArthur, Janet W.; Dobyns, Brown M.; Flukarty, Rex G., & Cope, Oliver [Mass. Gen. Hosp., Boston]: The functional activity of thyroid tumors, benign and malignant, as gauged by their collection of radioactive iodine. *West. J. Surg.* 56: 82-95, Feb., 1948.

Soley, Mayo H.; Lindsay, Stuart, & Dailey, Morris E. [Univ. Calif. M. Sch. & Hosp., San Francisco]: The clinical significance of a solitary nodule in the thyroid gland. *West. J. Surg.* 56: 96-104, Feb., 1948.

Vieta, John O. [N. Y. M. Coll., New York City]: Carcinoma of the thyroid and carcinoma of the testicle occurring in the same patient. *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* 10: 8-12, 1947.—Patient also has clinical findings of von Recklinghausen's neurofibromatosis.—*M. C. J.*

Ward, Robertson [San Francisco, Calif.]: California Cancer Commission Studies. Chapter

XV. Cancer of the thyroid. *California Med.* 68: 170-172, Mar. 1948.

FEMALE GENITAL TRACT

Costolow, William E. [Los Angeles Tumor Inst., Calif.]: Care of patients with advanced pelvic cancer. *Radiology* 50: 3-6, Jan., 1948.

Crossen, Robert J. [Washington Univ. M. Sch., St. Louis, Mo.]: The cancer potential in involuting organs. *Nebraska State M. J.* 33: 8-12, Jan., 1948.—In the detection of early cancerous and precancerous lesions of the female genital organs the aid of the general practitioner and the internist is essential to the gynecologist. Biannual examination of all women between 35 and 55 yrs. and others who have borne children is advised. The prevention of cancer of the female generative organs is based chiefly on the etiologic role of two factors: chronic irritation and involution. The effects of chronic irritation can be minimized by the active treatment of cervicitis, cauterization and coning of the cervix, total hysterectomy, or supravaginal hysterectomy and coning of the cervix. Vulvectomy is advised in leukoplakic vulvitis, because 50% of the cases develop into cancer. Since organs undergoing involutional changes are more susceptible to the development of cancer, particular recommendations are made regarding involutional ovaries and uteri. To discover early tumors of the ovary, notoriously asymptomatic until advanced, the author recommends periodic examinations, deep palpation via the vagina at every opportunity under anesthesia, and the removal of involuting ovaries when the abdomen is opened in women 42 yrs. or more. Radical surgery for such benign conditions as uterine myoma, pelvic endometriosis, nonmalignant ovarian enlargements, and the chronic inflammatory lesions of the uterus and adnexa, should be considered. In a study of 2662 cases of myoma, 526 irradiated and 2136 not irradiated, radiation as a substitute for surgery was found effective in relieving myoma symptoms in 90% and in reducing to one-third the risk of cancer developing later.

Two factors in the development of cancer of the endometrium—hyperplasia and delayed menopause or prolonged estrogen activity—are considered significant. Hyperplasia as a precursor of cancer is suggested by the clinical history of several curettages for hyperplasia in many patients found to have cancer and by the frequent finding of areas of hyperplasia along with cancer. Hyperplasia has been produced in mice and human castrates by the prolonged administration of estrogens, and more active hyperplasia has been observed in menopausal than in young mice. Clinically, many instances of cancer of the endometrium occurring simultaneously with granulosa-cell tumors of the ovary have been reported in recent yrs., and 2 studies have shown that fundal cancer is 4 times more frequent in women who menstruate beyond 50 yrs. The author advises that estrogen activity be stopped by radiation or surgery at 50 yrs. or

sooner if menstruation is abnormal, and suggests caution in the use of estrogenic substances at menopause and in cases of hyperplasia.—*S. A. Wilkins, Jr., M.D.*

Hall, J. Edward [Brooklyn Hosp., & Long Island Coll. Med., New York City]: Some highlights of obstetrical and gynecological pathology. *Brooklyn Hosp. J.* 6: 41-48, Jan., 1948.

Kernodle, John R.: Cuyler, W. Kenneth, & Thomas, Walter L. [Duke Univ. Sch. Med. & Hosp., Durham, N. C.]: The use of vaginal smears in the diagnosis of genital cancer. *North Carolina M. J.* 9: 11-17, Jan., 1948.—Papanicolaou technique; 4 illustrative case reports.

Rakoff, A. E. [Jefferson M. Coll. & Hosp., Philadelphia, Pa.]: The endocrine factors in pelvic tumors, with a discussion of the Papanicolaou smear method for diagnosis. *Radiology* 50: 190-201, Feb., 1948.

Schmitz, Herbert E., & Baba, George [Mercy Hosp.-Loyola Univ. Clinics, Chicago, Ill.]: Minor gynecologic surgery. *S. Clin. North America* 28: 222-227, Feb., 1948.

Torres, D. M. Gonzalez: Teste do esfregaço vaginal de Papanicolaou [sic] e Shorr. [Papanicolaou and Shorr vaginal smear test.] *Arq. de biol.* 31: 133-138, Nov./Dec., 1947.—A review.

VULVA

Brown, J. A. [Regina, Sask.]: Malignancy of the vulva. *Canadian M. A. J.* 58: 181-183, Feb., 1948.—The literature on cancer of the vulva is reviewed and 36 cases from the Regina Cancer Clinic analyzed. The most common type of cancer of the vulva (4% of genital cancers) originates from the epidermis; usually leukoplakic vulvitis with or without kraurosis is a predisposing factor. Early metastasis to lymph nodes—the most characteristic feature—was found in half, though often not suspected at the initial examination. The size of the primary tumor is not necessarily an indication of probability of metastasis. Metastases are generally limited to the regional areas; on autopsy only a few showed cancer extending to the aortic lymph nodes. Owing to the free anastomoses between the inguinal regions and the vulva, a unilateral removal of lymph nodes rarely results in a permanent cure.

The author prescribes a radical modified Basset operation followed by postoperative irradiation. If the complete Basset operation is done, the difference in survival between metastatic and nonmetastatic cases is only 11%, in contrast to cervix cancer where node metastases reduce cures by half. Irradiation is not recommended because: (a) vulvar cancer metastasizes early to lymph nodes where it cannot be completely destroyed by irradiation; (b) the skin of the vulva does not tolerate irradiation satisfactorily.

Twenty-seven of the 36 cases originated on the labium majus; 3 on the labium minus; 4

involved both the labia minora and majora; 2 occurred in the urethral region. Cancer of the vulva, pruritis, and leukoplakia coexisted in 24; 12 had cancer and pruritis; 2 had chronic urethritis. Treatment comprised: radical vulvectomy with bilateral groin dissection and post-operative irradiation, 21; radical vulvectomy and bilateral groin dissection, 2; radical vulvectomy and irradiation of regional node areas, 4; irradiation alone, 6; 3 refused treatment.

Two cases were less than 45 yrs. old; the rest, 45 to 75 yrs. Results are presented according to group classifications: *I.* Tumor not over 3 cm. in diameter, without groin nodes palpable: 12, alive; 1 dead of embolism. *II.* Tumor 4 to 7 cm., without palpable groin nodes, although 5 of the 8 showed pathologically positive nodes: 6, alive; 2, dead, although these 2 did not have the radical groin dissections. *III.* Tumor over 7 cm., with palpable node metastases: 5, dead; 3, alive. *IV* and *V.* More extensive disease: 7 dead.—*F. S. Butler, M.D.*

Crossen, Robert J. [Washington Univ., St. Louis, Mo.]: Primary carcinoma of Bartholin's gland. *Am. J. Surg.* 75: 597-600, Apr., 1948.—Case report.

Malpas, Percy [Univ. Liverpool, Eng.]: The prophylaxis of recurrent carcinoma of the vulva. *Acta radiol.* 28: 681-690, Nov., 1947.

Murphy, George H., & DuShane, James W. [Mayo Clin., Rochester, Minn.]: Mesodermal mixed tumor of the vagina: report of case. *Proc. Staff Meet., Mayo Clin.* 23: 22-24, Jan. 7, 1948.

Robertson, Edwin M. [Queen's Univ., Kingston, Ont.]: High lymphadenectomy and sympathectomy in carcinoma of the vulva. *Am. J. Obst. & Gynec.* 55: 79-85, Jan., 1948.—Case report: Three operations were done in 39 days on a 37-yr.-old female, with carcinoma of the vulva. These included a vulvectomy, an inguinal, pelvic, and lumbar lymphadenectomy, and a lumbar sympathectomy (as prophylaxis against arterial spasm and venous thrombosis). In addition, the reduction of excessive sweating reduced concomitant skin infection and helped promote better healing of the skin flaps.—*F. S. Butler, M.D.*

CERVIX

Adler, Ludwig [New York City]: Treatment of cervical cancer. *Acta radiol.* 28: 474-492, Nov., 1947.—After a survey of the history of surgery and radiotherapy in cervical cancer the author describes the "elective treatment" of this disease, which he used for more than 20 yrs.: extended vaginal operation with immediate insertion of Ra is performed in most cases; laparotomy with Ra insertion, in cases unfit for the vaginal operation, and irradiation, in inoperable cases and bad surgical risks. Permanent cures have been 39.4%. The primary mortality was 3.9% in the last 15 yrs.—*Auth. Summ.*

Ashton, Dorothy L. [Philadelphia, Pa.]: Carci-

noma of the cervix complicating procidentia uteri. *Am. J. Obst. & Gynec.* 55: 299-302, Feb., 1948.—Report of 2 cases.

Ashworth, C. T. & Diddle, A. W. [Parkland Hosp. & Southwest. M. Coll., Dallas, Tex.]: Anaplastic cervical epithelium. Relationship to cervical carcinoma. *South. M. J.* 41: 217-221, Mar., 1948.

Ayre, J. Ernest [Roy. Victoria Hosp., McGill Univ., Montreal, Que.]: Cervical cytology in diagnosis of early cancer. *J.A.M.A.* 136: 513-517, Feb. 21, 1948.

Connolly, Joseph P. [Stamford, Conn.]: Radiation therapy of carcinoma of the cervix. *Connecticut State M. J.* 12: 114-115, Feb., 1948.

Donaldson, Malcolm: The distribution of radiation in the treatment of carcinoma of the cervix. *Acta radiol.* 28: 769-775, Nov., 1947.—The necessity for an exact knowledge of the distribution of radiation is essential to the further advances in the treatment of carcinoma of the cervix by radium. A brief description of a vaginal and uterine applicator is given; it produces isodose curves far more advantageous than those of any applicator so far made.—*Auth. Summ.*

Ebenius, Bertil, & Sjövall, Alf [Univ. Lund, Sweden]: Parametritis as the first and only symptom of cervical carcinoma during pregnancy. *Acta radiol.* 28: 493-496, Nov., 1947.—Case report.

Fluhmann, C. F. [Stanford Univ. Sch. Med., San Francisco, Calif.]: A clinical and histopathologic study of lesions of the cervix uteri during pregnancy. *Am. J. Obst. & Gynec.* 55: 133-150, Jan., 1948.—Eighty-nine specimens obtained from the cervix uteri at all stages of gestation were studied histologically. All were removed because of lesions requiring biopsy or, (in 4) hysterectomy. Mucous polyps were found in 37; erosion, in 32; carcinoma, in 10; condyloma acuminata, in 5; endometrial polyps, in 3; and leukoplakia, in 2 cases. The histologic findings in so-called erosions most frequently showed increase in number of cervical glands with high columnar epithelium, the formation of cystic structures lined by cuboidal epithelium, papillary outgrowths covered by cylindrical epithelium, edema and increased vascularity, increased activity of the basal layer of squamous epithelium, and epidermoidization. Isolated islands of decidua were present in 11 cases; inflammatory changes, absent in 11.—*J. P. Wozencraft, M.D.*

Graham, Ruth M.: Sturgis, Somers H., & McGraw, John [Vincent Memorial Hosp.: Mass. Gen. Hosp., Boston]: A comparison of the accuracy in diagnosis of the vaginal smear and the biopsy in carcinoma of the cervix. *Am. J. Obst. & Gynec.* 55: 303-307, Feb., 1948.—A comparison of the diagnostic accuracy of the vaginal smear and the standard biopsy technique has been made in 181 cases of epidermoid

carcinoma of the cervix. The first biopsy report was correctly positive in 90% of the series. The first vaginal smear report was positive in 91% of the same cases. By a combination of the two methods, the correct diagnosis was initially obtained in 178 cases, or approximately 99% of the group. The vaginal smear was more accurate than the biopsy in diagnosing the early carcinomas of the cervix in this series of cases. From this study of cervical cancer we conclude: (1) that the vaginal smear is diagnostically as reliable as the biopsy taken in a large general hospital; (2) that an extremely high percentage of cases can be diagnosed accurately if the two methods are used together; and finally, that the vaginal smear is of special value in the diagnosis of the very early malignant lesions of the cervix.—*Auth. Summ.*

Grenier, E. P. [Inst. Radium, Montreal, Que.]: New apparatus for radium treatment of cancer of the uterine cervix. *Canadian M. A. J.* 58: 192-193, Feb., 1948.

Hill, Adrian [Lymington & District Hosp., Eng.]: Gross hypertrophy of the pregnant uterine cervix simulating cancer. *J. Obst. & Gynacc. Brit. Emp.* 55: 31-35, Feb., 1948.—Case report.

Holzaepfel, J. H., & Reel, P. J. [Ohio State Univ. Coll. Med., Columbus]: Carcinoma of the cervix in the young age group. *Ohio State M. J.* 43: 1047-1049, Oct., 1947.

Ingelman-Sundberg, Axel [Radiumhemmet, Stockholm, Sweden]: Rectal injuries following the Stockholm method of treatment of cancer of the cervix uteri. *Acta radiol.* 28: 760-764, Nov., 1947.

Jacoby, P. [Radiumcenter, Odense, Den.]: The experiences with radiotherapy in cancer of the cervix and of the corpus of the uterus at the Radiumcenter in Odense. *Acta radiol.* 28: 505-518, Nov., 1947.—Results of radiological treatment from 1928-1941 are: Cancer of the cervix: 373 patients, examined; 365, treated. 120 were free of evidence of disease after 5 yrs.—absolute cure rate, 32.2%; relative, 32.9%. Cancer of the corpus: 98 patients, admitted for treatment, but only 92 treated; 25 treated with Heyman's packing method. The relative cure rate for all patients treated is 38% and for the clinical operable cases, 66.5%.—*Auth. Summ.*

Kahanpää, V., & Kankkunen, J. O. [Zentralinst. f. Strahlentherap., Helsinki, Fin.]: Über die Behandlungsergebnisse der Kollumkarzinome im Strahlenbehandlungsinstitut zu Helsinki aus den Jahren 1937-1942. [Results of treatment of carcinoma of the cervix in the Institute for Irradiation of Helsinki for the years 1937-1942.] *Acta radiol.* 28: 519-530, Nov., 1947.—The material comprises 524 cases of cervix carcinoma (from 1937 to 1942); only 35% were favorable—stages I & II. The 58 worst cases were dismissed without palliative treatment. The remaining 466 cases have been treated in accordance with the principles of the Stockholm method. The Ra dose was on the

average ut. 3300 and vag. $4710 \approx 8010$ mg./hr. The calculated deep x-ray dose was 2440 r to both parametria. Primary mortality was $2.8 \pm 0.8\%$, absolute recovery $31.9 \pm 2.0\%$, and relative recovery by stages: I, 88%; II, 54%; III, 26%; and IV, 6%; I-IV, $35.8 \pm 2.2\%$. In all cases treated the diagnosis was histologically confirmed. The prognosis depends on the stage and, on the whole, the clinical picture. The histological structure of the tumor seems to have no special influence on the prognosis. The results obtained favor a principally radiological treatment of the cervix carcinomas of stages I and II also.—*Auth. Summ.*

Kaplan, Henry S.; Wilson, Hugh M., & Morse, Arthur H. [Yale Univ. Sch. Med., New Haven, Conn.]: Results and causes of failure of radiation therapy in carcinoma of the cervix. *Surg., Gynec. & Obst.* 86: 332-340, Mar., 1948.—The results in 88 patients with carcinoma of the cervix treated by combined x-rays and radium in a general hospital have been reviewed. The net 5-yr.-survival rate was 38%, which compares favorably with that reported elsewhere. However, almost all the 5-yr. survivals occurred in the disproportionately large group of "operable" stage I and II cases: results in more advanced cases were thus unsatisfactory. Possible technical modifications which might yield better results are discussed. It is concluded that the interval between x-ray and Ra therapy should be shortened from 6 wks. to 2 wks. or less; Ra dosage, increased somewhat in advanced cases; the "Manchester technique" of radium application, adopted; and that extra-peritoneal iliac lymphadenectomy, performed after irradiation in stages I, II and III to save patients with regional lymph-node involvement.—*Auth. Summ.*

McGoogan, Leon S. [Omaha, Nebr.]: The early diagnosis of carcinoma of the cervix and of the corpus uteri. *Rocky Mountain M. J.* 45: 206-208, Mar., 1948.—A review.

Michaels, John P. [Sch. Med., Tulane Univ., New Orleans, La.]: Study of ureteral blood supply and its bearing on necrosis of the ureter following the Wertheim operation. *Surg., Gynec. & Obst.* 86: 36-44, Jan., 1948.

Mitra, Subodh [Carmichael M. Coll., Calcutta, India]: The evaluation of the results of carcinoma of the cervix uteri treated by radical vaginal operation. *Am. J. Obst. & Gynec.* 55: 293-298, Feb., 1948.

Nordmann, Marius [Fribourg, Switz.]: Un moyen de diagnostic précoce du cancer du col de l'utérus: la colposcopie. [A means for early diagnosis of cancer of the cervix: colposcopy.] *Rev. gén. de clin. et de thérap.* 61: 397-399, Sept. 4, 1947.

Petersen, Ekkert [Hôp. de l'État à Sønderborg, Den.]: Trois cas de cancer du col utérin pendant la dernière moitié de la grossesse. [Three cases of cervical cancer occurring during the last half of pregnancy.] *Acta*

- radiol. 28: 542-544, Nov., 1947.—Report on 3 cases of cancer of the cervix during advanced pregnancy, given exclusive local treatment with radium emanation. Parturition occurred without any considerable difficulty. 2 cases, under control, have not recurred for 7 yrs. In both cases, menstruation did not cease, and, in one of them, another parturition occurred later on. Children are developing normally.—*Auth. Summ.*
- Posey, Louis C., & Cunningham, Joseph A. [M. Coll. Ala., Birmingham]: Impressions of the vaginal smear technic in the diagnosis of cervical cancer. *South. M. J.* 41: 221-228, Mar., 1948.—Of 3808 smears from 1435 patients, 13 were reported positive; 42, doubtful; and 1381, negative. Biopsy showed cancer in 4, negative by smear examination. In the 13 positive smears, proof was obtained in 9, 2 were not traced, and the other 2 were false positives ascribed to lack of appreciation of the significance of cell changes—one being negative on repeat examination and one having had irradiation for cervical carcinoma 8 yrs. previously. The positive smears have been most obvious. The problematic smears are those where there is doubt as to the significance of cell changes. The confusion is greatest in patients with low estrogen levels plus infection. The only practical criteria in smears are cellular pleomorphism and basophilia. The rate of desquamation of the cancer cells is a function of the surface area and hence may be hidden by dilution. The smear method is particularly applicable in endocervical carcinoma.
- The impracticability of the method as a screening test is pointed out: if every woman more than 30 yrs. were examined biannually 70,000,000 examinations would be required, of at least 5 min. each or 5,800,000 examining hrs. If the 1500 pathologists in the country examined smears 300 eight-hour days a year, approximately one-half the required examinations would be completed.—*M. W. Stearns, M.D.*
- Pund, Edgar R.; Nieburgs, H. E.; Nettles, J. B., & Caldwell, J. D. [Univ. Ga. Sch. Med., Augusta]: Preinvasive carcinoma of the cervix uteri. Seven cases in which it was detected by examination of routine endocervical smears. *Arch. Path.* 44: 571-577, Dec., 1947.
- Regato, J. A., del [Ellis Fischel State Cancer Hosp., Columbia, Mo.]: The role of the transvaginal roentgentherapy in the treatment of carcinoma of the cervix. *Surg., Gynec. & Obst.* 86: 480-486, Apr., 1948.—Discussion of apparatus, technique, and results—44% 3-yr. symptom-free survival in 76 cases.
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- Swanberg, Harold [Editor, Miss. Valley M. J. & Radiol. Rev., Quincy, Ill.]: Summary of results in the radiation treatment of uterine cervical cancer. A statistical study of volume 4 of the League of Nations "Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix," edited by Prof. J. Heyman; statement of 5 year end-results of 1,796 patients whose treatment began in 1933. *Acta radiol.* 28: 554-563, Nov., 1947.
- Tod, Margaret C. [Holt Radium Inst., Manchester, Eng.]: Optimum dosage in the treatment of cancer of the cervix by radiation. *Acta radiol.* 28: 564-575, Nov., 1947.
- Ward, George Gray [New York City]: The treatment of carcinoma of the cervix complicated by pregnancy. *Acta radiol.* 28: 576-582, Nov., 1947.—Adequate speculum examination of cervix and vagina should be made in every pregnancy, and a biopsy made in every suspicious case. Irradiation of the cervix by radium and high-voltage x-rays with supracervical hysterectomy and bilateral salpingo-oophorectomy is best for cervical carcinoma complicated by pregnancy. In the nonviable cases, a supracervical hysterectomy should be done immediately, sacrificing the fetus, and as soon as recovery warrants, irradiation of the cervix stump followed by high-voltage x-ray therapy, thus avoiding the trauma to the cervix in evacuating the uterus, and the danger of disseminating the cancer cells, also obtaining the benefit of the retarding factor resulting from the castration. In pregnancy seen at the 6th mo. where a child is anxiously desired, [minimum] irradiation of the cervix may be done before hysterectomy in the hope of getting a living child. In all viable cases a Porro-caesarian section should be first done, followed by irradiation of the cervix stump and high-voltage x-ray therapy.—*Auth Summ.*
- Wyatt, James [Chairman]: Joint discussion No. 3. Discussion on some aspects of surgical and radiological treatment of carcinoma of the cervix. *Proc. Roy. Soc. Med.* 40: 907-922, Dec., 1947.

UTERUS

Acosta-Sison, H. [Univ. Philippines, Manila]: Dangers of myometrial chorioepithelioma caused by failure of early diagnosis. *Philippine J. Surg.* 2: 240-246, Nov./Dec., 1947.

Arneson, A. N.; Stanbro, William W., & Nolan, James F. [Edward Mallinckrodt Inst. Radiol.: Washington Univ. Sch. Med., & Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: The use of multiple sources of radium within the uterus in the treatment of endometrial cancer. *Am. J. Obst. & Gynec.* 55: 64-78, Jan., 1948.—In 1938 the method of radium treatment at the Barnes Hospital and the Barnard Free Skin and Cancer Hospital was changed

- from one employing *intrauterine tandems* to a technique using *multiple capsules* of Ra packed individually into the uterine cavity. The plan is a modification of the Heyman packing method, whereby an introducer is utilized to increase the number of tubes placed within the uterus. The length of the brass capsules varies, but the strength per cm. active length is on the order of 5 or 6 mg. Ra. Patients also receive a course of external x-rays prior to Ra. The authors review 93 cases treated from 1936 through 1941, and attempt to compare the relative effectiveness of both methods. Reference is made to comparative results obtained from the literature. The group was treated as follows: irradiation alone, 43; irradiation and hysterectomy, 32; hysterectomy alone, 18. The 5-yr. survivals were 27%, 68%, and 84%, respectively, with a 53% survival for the entire series. The high survival rate for hysterectomy alone is attributed to selection of favorable clinical material. Variation in survival rate with histological type shows that better results were obtained in the more highly differentiated forms. Among patients treated by irradiation alone, the well-differentiated lesions show for tandems and multiple capsules values of 25% and 36%, respectively; for the undifferentiated tumors, 16% and 28%. Variation in survival rate was found also with the size of the uterus; a few patients with uterine enlargement showed better results with multiple capsules. Of those treated by irradiation alone, the use of intrauterine tandems in 18 cases resulted in a 22% survival; with multiple capsules, used in 25 cases, 32% survived. With treatment by irradiation and hysterectomy the 5-yr.-survival rate is 54% with tandems, and 79% with multiple capsules. Persistent tumor was found in 77% of surgical specimens irradiated by tandems, against 26% where multiple capsules were employed, and of 32 patients treated by hysterectomy after the use of x-rays and Ra, 47% showed persistent tumor with a 46% survival; where no tumor was identified, the survival rate was 88%. 11 patients received as high as 5000 and 7000 mg.-hr. by multiple capsules, and although an intense reaction was produced, areas of severe damage and necrosis were rarely found. Hysterectomy was performed at varying intervals of time after Ra treatment, and in those where 6 wks. intervened, there was evidence indicating recovery and renewed growth of tumor not destroyed completely. There is risk of uterine perforation when multiple capsules are used (2 cases).—F. S. Butler, M.D.
- Bradley, E. Tremain [New Canaan, Conn.]: Results of treatment of carcinoma of the body of the uterus. Connecticut State M. J. 12: 112-113, Feb., 1948.
- Casas, Pedro Figueroa: Presentación de radiografías y pieza operatoria caso de uterolitos. [Presentation of x-rays and operative specimen of a uterolith.] Bol. Soc. de obst. y ginec. de Buenos Aires 26 (13): 495-498, 1947.—Calcification of a myoma.
- Costolow, William E. [Los Angeles Tumor Inst., Calif.]: Gynecologic aspect of cancer. Ann. West. Med. & Surg. 2: 120-121, Mar., 1948.
- Cox, John Kenneth [Baylor Hosp., Dallas, Tex.]: The value and accuracy of the vaginal smear in the diagnosis of uterine and cervical cancer. Texas Rep. Biol. & Med. 6: 77-86, Spring, 1948.
- Davies, D. V. [Cambridge Univ., Eng.]: A benign tumour of the placenta. J. Obst. & Gynaec. Brit. Emp. 55: 44-46, Feb., 1948.—Case report [chorioangioma].
- Falls, Frederick H. [Chicago, Ill.]: Carcinoma and uterine fibromyomas. J. Internat. Coll. Surgeons 11: 24-28, Jan./Feb., 1948.
- Ferrari, Roberto A., & Colotta, Francisco: Angioma de la placenta. [Placental angioma.] Bol. Soc. de obst. y ginec. de Buenos Aires 26 (13): 484-488, 1947.—Case report.
- Gates, Olive, & Warren, Shields: A Handbook for the Diagnosis of Cancer of the Uterus by the Use of Vaginal Smears. Cambridge. Harvard Univ. Press. 1947. 182 pp. \$4.00.
- Haines, Magnus [Chelsea Hosp. for Women, London, Eng.]: Solitary adenomyoma of the uterus. J. Path. & Bact. 59: 691-694, Oct., 1947.—Case report.
- Hoed, D. Den [Rotterdamsch Radiotherap. Inst., Rotterdam, Holland]: Methods to reduce the dangers of radiotherapy in cancer of the uterus. Acta radiol. 28: 497-504, Nov., 1947.
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- Martindale, L. [New Sussex Hosp. & Marie Curie Hosp., London, Eng.]: A clinical review of 262 cases of cancer of uterus. Acta radiol. 28: 531-541, Nov., 1947.—In 1945 the population of England and Wales was 38,157,000. Of this census, 74,291 deaths were due to cancer, and within this group, 4372 died of cancer of the uterus; 7294, of cancer of the breast. During the war, radium and x-ray therapy were impossible at times, due to air bombardments. Of the 174 cases of cervix cancer seen to the end of 1946, panhysterectomy was done in 23 (15 followed by x-rays), deep x-rays in 6, Ra treatment to 138 cases, while 7 were not treated. The age incidence was 27 to 77 yrs. Since 1925, 136 were treated with Ra according to the Marie Curie Hospital technique: stage I, 5; stage II, 43; stage III, 66; stage IV, 22.
- The technique described for treating cervix cancer includes an intra-uterine tandem which contains two 3-cm. tubes, each containing 25 mg. Ra (an extra tube is added if the uterine cavity measures over 7 cm.). Vaginal plaques

(each containing 4-5 mg. needles) are placed at the same time, one in each lateral fornix and the third directly over the cervix. The vagina is finally packed with gauze wrung out in acriflavine. The total dosage was given in 66 hrs., divided into 3 equal treatments at intervals of 1 or 2 wks. The average total dosage was 7261 mg.-hr. The 5-yr.-survival rate of 4 cases of stage I was 100%; 40 of stage II, 55%; 61 of stage III, 29.5%; and 16 of stage IV, 0%. 4 developed rectovaginal fistulas; there was 1 vesicovaginal fistula.

The treatment of 88 cases of cancer of the corpus uteri seen to the end of 1946 (the author mentions that this was a relatively large proportion for his series) comprised hysterectomy in 51, radiotherapy in 33, and a laparotomy in 4. Within the hysterectomy group, a subtotal was done in 12, and a panhysterectomy in 39 cases. Of the 12 receiving subtotal operations, 1 died of cardiac failure postoperatively, 2 lived less than 5 yrs., 2 were not traced, and 7 are alive and well after 5 yrs. The 5-yr.-survival rate for the surgically treated patients was 50.9%. In 2 cases a resection and anastomosis was done where adherent diseased colon was found. Both patients are well, 1 after 8 yrs., the other after 13. Ra was used to treat 33 cases of corpus cancer, and in 4, pyometra with pyrexia was present or developed after 1 or 2 treatments. The technique in a typical case consisted of the placement of an intra-uterine tandem of 2 tubes, each 3 cm. long containing 25 mg. Ra (an extra tube is added if the uterine cavity measures longer than 7 cm.). Before placing the intra-uterine tubes in position, 2 small tubes 1.1 cm. in length, each containing 8 mg. Ra and mounted on long wires, are placed in the uterus, extending transversely from the top of the central tandem to the cornua. 2 vaginal plaques, each containing 20 mg. Ra, are placed in position in each lateral fornix, and the vagina is finally packed with acriflavine-soaked gauze. The Ra is left in situ for 66 hrs. and divided into treatments as described above, a total of 6996 mg.-hr. being the average dose given. The 5-yr. survival for this group was reported to be 54.5%. The 5-yr. survival of all 88 cases of cancer of the corpus uteri treated by surgery or radiotherapy was 50%. In this same group, fibromyomata occurred in 12. In 6 cases, cancer of the uterus was either preceded or followed by a primary cancer in some other organ.—*F. S. Butler, M.D.*

Mussey, Elizabeth; Dockerty, Malcolm B. & Masson, James C. [Mayo Clin., Rochester, Minn.]: Malignant lesions of the uterus associated with estrogen-producing ovarian tumors: report of two cases. *Proc. Staff Meet., Mayo Clin.* 23: 63-70, Feb. 4, 1948.

Nolan, James F. [St. Louis, Mo.]: The physiological characteristics of uterine cancer in relation to radiation therapy. *Journal-Lancet* 68: 1-5, Jan., 1948.—A review.

Novak, Emil, & Rutledge, Felix [Johns Hopkins M. Sch., Baltimore, Md.]: Atypical endome-

trial hyperplasia simulating adenocarcinoma. *Am. J. Obst. & Gynec.* 55: 46-63, Jan., 1948. —The lesions described are characterized by an increased number of glands with little intervening stroma, stratification of the cells lining the glands, areas of epidermoidization, and absence or sparsity of cystic glands. One group, 18 patients, remained well after curettage, curettage followed by x-rays, or radium menopause. 1 had postsurgical menopause but had received stilbestrol for many months. Curettage revealed atypical endometrial hyperplasia. After stilbestrol had been discontinued for a month, curettage showed atrophic endometrium. The second group comprised 26 patients with atypical hyperplasia found on curettage. In these, hysterectomy was performed without preceding irradiation. No gross lesions were found; some showed focal, others diffuse, hyperplasia. The regular cells and small nuclei of atypical hyperplasia comprise the chief cytologic difference between it and carcinoma of the endometrium. In a few cases the benign nature of the lesions was uncertain microscopically; such cases should be treated as carcinoma.—*J. P. Wozencraft, M.D.*

Owen, May [Terrell's Labs., Fort Worth, Tex.]: The persistent positive Friedman test in hydatid moles. *Texas State J. Med.* 43: 582-585, Jan., 1948.

Pernworth, Paul [St. Elizabeth's Hosp., Granite City, Ill.]: Chorioncarcinoma. *Am. J. Surg.* 75: 521-523, Mar., 1948.—Case report.

Richter, Kurt [II. Univ.-Frauenklin., Vienna, Austria]: Zur Klinik des Uterussarkoms. [Sarcoma of the uterus.] *Krebsarzt* 3: 91-101, Mar., 1948.—The author reports 49 cases of sarcoma of the uterus: 30, arising in myoma; 7, diffuse; 4, cervical; 4, mucosal; 4, site of origin unknown. Preoperative diagnoses were made in 10% of sarcomas in myomas: 28.5%, wall sarcomas; 50%, mucosal; 75% of those of unknown site of origin and of the cervix. Diagnosis became easier the closer the sarcoma came to the uterine cavity or to the cervix; usually these diagnoses were dependent on biopsy or smear. 38 were operated upon, 33 radically. 43 were followed for more than 5 yrs. Of 34 operated upon, 17 had 5-yr. cures: 11 succumbed (4 primary operative): 6 were lost; none of the 9 treated by x-rays or radium had a 5-yr. cure. In all, 17 lived longer than 5 yrs., 20 died, 6 were lost. The absolute cure rate was 39.5%. The histological diagnosis of each case is given.—*M. C. J.*

Sylvén, Bengt [Radiumhemmet, Stockholm, Sweden]: Myogenic sarcomas of the uterus with skeletal metastases. *Acta radiol.* 28: 691-696, Nov., 1947.

Vara, Paavo, & Bardy, Anja [Second Women's Clin., Univ. Helsinki, Fin.]: Myoma of uterus complicating pregnancy and labour. *Ann. chir. et gynaec. Fenniae* 36 (3): 193-218, 1947.

Vesper, Albert J. [Covington, Ky.]: Uterine bleeding with view toward conservative pelvic surgery. *Kentucky M. J.* 46: 38-44, Feb., 1948.

- Warrenburg, Clarence B. [Phoenix, Ariz.]: Hydatidiform mole followed by chorionepithelioma. *Arizona Med.* 5: 57-60, Jan., 1948.—Case report.
- Williams, George A., & Stewart, Calvin B. [Grady Hosp., & Emory Univ. Sch. Med., Atlanta, Ga.]: Aspiration curettage of the endometrium in a cancer clinic. An analysis of 200 cases. *Am. J. Obst. & Gynec.* 54: 804-808, Nov., 1947.—At the Steiner Cancer Clinic of the Emory School of Medicine, aspiration curettage of the endometrium was performed in 200 cases with pre- and postmenopausal abnormal genital bleeding. No anesthesia or hospitalization was required. An insufficient amount of tissue to make a diagnosis was obtained in 12%; 6.5% had atrophic endometrium—regarded as undiagnosed. The final diagnoses in many required prolonged observation. The results of aspiration curettage were checked in 35 by surgical dilatation and curettage or hysterectomy; 80% agreement was found. A diagnosis of cancer was made in 22 of the entire group. The authors believe that aspiration curettage has value as a screening measure in a cancer clinic. In addition, it is readily accepted by the patient and can relieve the pressure for hospitalization, especially when insufficient facilities are available for cases of this type.—C. A. Waltman, M.D.
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- Wyatt, James [St. Thomas's Hosp., Eng.]: Testosterone propionate in inoperable carcinoma. *J. Obst. & Gynaec. Brit. Emp.* 55: 53-54, Feb., 1948.—Case report; uterine carcinoma.
- Zilliacus, Harry [Univ. Helsinki, Fin.]: A dosimeter for preventing radiation injuries to the rectum during treatment of carcinoma of the uterus with radium. *Acta radiol.* 28: 790-795, Nov., 1947.
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- Baravalle, Norberto: Cistoadenoma papilar del ovario. [Papillary cystadenoma of the ovary.] *Bol. Soc. de obst. y ginec. de Buenos Aires* 26 (13): 519-526, 1947.
- Bettinger, H. F., & Jacobs, Hubert [Melbourne, Australia]: Mesonephroma ovarii. *M. J. Australia* 1: 100-104, Jan. 24, 1948.—Case report and survey of the literature.
- Brewer, A. C. [Liverpool Roy. Infirmary, Eng.]: Granulosa-cell tumour of ovary as acute abdominal emergency. *Brit. M. J.* 1: 49, Jan. 10, 1948.—Case report.
- Chalmers, J. A. [Roy. North. Infirmary, Inverness, Scotland]: Fibromyoma of the fallopian tube. *J. Obst. & Gynaec. Brit. Emp.* 55: 155-158, Apr., 1948.—Case report.
- Donato, Vicente Marino: Cancer primitivo de la trompa. [Primary cancer of the fallopian tube.] *Bol. Soc. de obst. y ginec. de Buenos Aires* 26 (13): 488-494, 1947.—Case report.
- Harris, William [Mt. Sinai Hosp., New York City]: Malignant teratomas and some remarks on their radiosensitivity. *Acta radiol.* 28: 633-637, Nov., 1947.—Discussion and report of 6 cases.
- Karen, Benjamin, & Kushner, J. Irving [Bronx Hosp., New York City]: Dysgerminoma of the ovary. *Am. J. Obst. & Gynec.* 55: 337-339, Feb., 1948.—Case report.
- McGarrity, K. A., & Dodson, L. F. [Sydney, Australia]: Struma ovarii accompanied by thyreotoxicosis. *M. J. Australia* 1: 42-44, Jan. 10, 1948.
- Norwood, G. E. [Huntington Memorial Hosp., Pasadena, Calif.]: Struma ovarii. *Ann. West. Med. & Surg.* 2: 19-21, Jan., 1948.
- Novak, Emil [Johns Hopkins M. Sch., Baltimore, Md.]: Tumores ováricos con función hormonal sexual. [Ovarian tumors with sex-hormone function.] *Ginec. y obst., México* 2: 407-420, Nov./Dec., 1947.
- Raurama, Mauno [Univ. Helsinki, Fin.]: Carcinoma of the ovary developing on the basis of ovarian endometriosis. *Acta radiol.* 28: 638-643, Nov., 1947.—The histologically examined case, elucidated by microphotographs, seems to support the opinion that endometriosis can degenerate into carcinoma.—Auth. Summ.
- Reiner, Walter C. [Portland, Oreg.]: Gigantic ovarian cyst developing in a thecoma. Problem encountered in surgical management. *West. J. Surg.* 56: 205-207, Apr., 1948.—Case report.
- Rosenfeld, Samuel S. [Lebanon Hosp., New York City]: A pseudomucinous cyst of the ovary with ascites and hydrothorax. *New York State J. Med.* 48: 527-528, Mar. 1, 1948.—Case report.
- Sans, Pedro A., & Paredes, Héctor Fernández: Teratoma adulto del ovario espontaneamente perforado. [Spontaneous rupture of a teratoma of the ovary.] *Bol. Soc. de obst. y ginec. de Buenos Aires* 26 (13): 505-512, 1947.
- Santesson, Lars [Radiumhemmet, Stockholm, Sweden]: Clinical and pathological survey of ovarian tumours treated at Radiumhemmet. I. Dysgerminomas. *Acta radiol.* 28: 644-668, Nov., 1947.—From 700 cases of ovarian tumors collected up to the end of 1940 at Radiumhemmet and classified by the author, a summary of the clinical records of 37 cases of pure dysgerminoma is presented; 5-yr. results are available for 27. Nearly all were operated upon elsewhere, then referred to the Radiumhemmet. The data on 192 cases assembled from a review of the literature are also included. The leading symptoms were abdominal swelling, evidence of a mass in the lower abdomen, pain, and loss of weight. Although the duration of symptoms was usually less than 4 mos., in 31

cases the tumor was at least the size of a man's fist. Predominantly, the tumor affects those less than 30 yrs. old (81%). Pseudohermaphroditism, hypogenitalism, and other forms of sexual maldevelopment coexisted in two cases only: infantile uterus and uterus subseptus.

These tumors metastasize predominantly through the intraligamentary lymphatics, first to the retroperitoneal lymph nodes along the abdominal vessels, later to the mediastinal nodes. Metastases also occur to the lung, liver, pancreas, spleen, and kidney. Bone metastases are described by other authors; hematogenic dissemination is considered rare. Rupture of the capsule may occur spontaneously or at operation and is serious. In 8 cases where this occurred before operation, 5 died; the other 3 had peritoneal implantation metastases at operation. The only living case was operated upon 2½ yrs. ago. Hormonal assays were not done. The dysgerminoma is sometimes bilateral. An analysis of 169 cases, including the present series and those in the literature, shows that 51% occur in the right ovary; 32%, in the left; and 17% are bilateral.

Treatment of choice is radical surgical removal followed by radiotherapy. Since these tumors show great x-ray sensitivity, postoperative radiological treatment should be used as a prophylactic measure against recurrences. A survey of limited material suggests that if the unaffected ovary is left at operation and is not irradiated, the recurrence rate in this ovary is high. The number of cases in the literature followed more than 5 yrs. is rather small, but of those collected plus the author's 27 (a total of 107 cases), the survival rate is 51.4% (55 cases). The rate for the cases at Radiumhemmet is 18 of 27 (66.7%). Of 48 cases in the literature with follow-up data that had operation only, without radiological treatment, 20 (41.7%) survived more than 5 yrs. The prognosis in cases with bilateral disease is very grave. Of 14 cases in the literature, only 5 are living after a 3-yr. follow-up.—*F. S. Butler, M.D.*

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Speck, George [Bellevue Hosp., & N. Y. Univ. Coll. Med., New York City]: A clinical review of papillary adenocarcinoma of the ovary. *Virginia M. Monthly* 75: 185-190, Apr., 1948.—Analysis of 25 cases.

Ward, Lawrence S., & Henkle, Robert T. [Home Memorial Hosp., New London, Conn.]: Teratoma of the ovary, removal with subsequent pregnancy. *Connecticut State M. J.* 12: 215-217, Mar., 1948.—Case report.

GENITOURINARY TRACT

KIDNEY AND URETER

Chapman, Milran A. [Memorial Hosp., Pawtucket, R. I.]: Wilms tumor. Report of two

cases in the same family. *Rhode Island M. J.* 31: 105-106; 109, Feb., 1948.

Chenery, Alan J., & Benson, Alfred H.: Cavernous hemangioma of the kidney. *J. Urol.* 59: 164-166, Feb., 1948.—Case report.

Dawley, Walter A. [Rapid City, S. Dak.]: Renal tumor. *South Dakota J. Med. & Pharm.* 1: 144-153, Apr., 1948.—Report of 5 cases.

Foot, N. Chandler, & Humphreys, Gustavus A. [Cornell Univ. M. Coll., New York City]: The importance of accurate pathologic classification in the prognosis of renal tumors. *Surgery* 23: 369-376, Mar., 1948.—This study is based on 58 cases of renal tumors. The following classification of renal tumors is suggested: (A) tumors derived from mesodermal renal cap—simple adenoma; renal-celled carcinoma, including some tubular forms; (B) tumors derived from ectodermal outgrowth from cloaca—transitional-celled papilloma; transitional-celled carcinoma, epidermoid carcinoma, and some tubular carcinomas (of collecting tubules); (C) tumors derived from embryonal tissue such as mesonephros—embryonal carcinoma (juvenile and adult forms), mixed embryonal tumors, including that of Wilms; (D) tumors derived from perirenal capsule—fatty, connective tissue, muscular and nervous tissue growths. Stoerk's observations ". . . that there is no convincing similarity between tumors derived from suprarenal or renal tissue, . . . that the most variable forms of Grawitz tumor prove to be histological variants of the same arch type and . . . that Grawitz tumors of the kidney are of nephrogenic origin" are reiterated.

The survival figures for 42 patients having nephrectomy prior to 1943 are given. Renal-celled tumors were by far the most common group and offered the best prognosis for 5-yr. survival. In all other groups of malignant renal tumors the prognosis was poor. Within the renal-celled group a definite correlation was found between the histologic picture and the prognosis. The relatively nonmalignant renal-celled tumor showed: solid cords of large, clear cells with nuclei usually small, and regular in size and shape; usually heavy septa of connective tissue; little microscopic evidence of hemorrhage and inflammation; definite delimitation from surrounding tissue. The malignant type showed: cells of variable size often arranged in tubular or papillary patterns; anisometric nuclei and frequent mitotic figures; poorly formed septa infiltrated by lymphocytes or polymorphonuclear leucocytes; hemorrhage and necrosis.

[In calling attention to Stoerk's assertion of the fundamental nephrogenic origin of all Grawitz tumors and in presenting a simple classification of renal neoplasms meeting both clinical and pathologic needs and having prognostic significance, the authors have significantly clarified the subject of renal tumors. The position of the true hypernephroma (renal tumor of adrenal tissue) is not clear in the suggested classification and the assertion that transitional-celled

tumors are of entodermal origin is certainly at variance with most present opinion on this subject.]—*W. F. Whitmore, M.D.*

Fuchsman, Jacob J., & Angrist, Alfred [Queens Gen. Hosp., Jamaica, N. Y.]: Benign renal tumors. *J. Urol.* 59: 167-173, Feb., 1948.

Hale, Nathan G. [Sacramento, Calif.]: Primary papillary carcinoma of the ureter: report of two cases. *Urol. & Cutan. Rev.* 52: 3-7, Jan., 1948.

Macalpine, Jas. B. [Manchester, Eng.]: Bilateral renal papillomata: two cases. *Brit. J. Surg.* 35: 132-134, Oct., 1947.

Macalpine, Jas. B. [Manchester, Eng.]: A case in which two dissimilar growths, an adenoma (adenocarcinoma) and a papillo-carcinoma, occurred in the same kidney. *Brit. J. Surg.* 35: 134-136, Oct., 1947.

Macalpine, Jas. B. [Manchester, Eng.]: Papilloma of the renal pelvis in dye workers: two cases, one of which shows bilateral growths. *Brit. J. Surg.* 35: 137-140, Oct., 1947.

Macalpine, Jas. B. [Manchester, Eng.]: Papillomatous disease of the renal pelvis. *Brit. J. Surg.* 35: 113-132, Oct., 1947.—Seventeen cases of papillomatous disease of the renal pelvis (10 benign, 7 malignant) are reviewed for pathology, symptomatology, treatment, and results; solid or nonpapillomatous tumors are excluded. Discrepancies between the clinical behavior and the pathological diagnosis of papillary tumors are discussed. The author lists the following points as beyond question: (1) A papilloma may be benign in one part and malignant in another. (2) Pathologically benign tumors may behave clinically as carcinoma, presumably because a focus of carcinoma escaped observation. (3) Pathologically unfavorable tumors may remain well, possibly representing true surgical cures. (4) The primary tumor may be malignant and the satellites benign. (5) The primary tumor may be benign and the satellites malignant. (6) A growth may be benign in its early stages but become malignant later. (7) Secondary deposits do not necessarily resemble the primary focus. (8) Whenever papillomatous material is implanted in a wound, whether the growth in its original situation be benign or malignant as appraised clinically and pathologically, the implant will behave as a malignant one. The author further believes that implants are always transferred with the stream of urine, never from below upwards, except in the event of a hydronephrosis. Hematuria dominated the clinical picture but pain and tumor occasionally were noted. Cystoscopy, renal-function tests, and pyelography were useful diagnostic procedures. Stone was observed in 2 cases, and stone, infection, and obstruction in relation to renal pelvis tumors are briefly discussed. One-stage juxtavesical nephro-ureterectomy followed by perurethral fulguration of the intramural ureteral stump is considered the treatment of choice, but this plan is modified to fit special circumstances. Other methods of treatment are discussed.

Of the 10 patients with benign papillomas, 8 were alive and well from 2 to 23 yrs. post-operatively. The other 2 had local recurrences presumably due to operative sowing and died 10 and 11½ yrs. after their first symptoms. Of the 7 with malignant tumors, 6 are dead, and 1 is alive and well 6 yrs. postoperatively. In 2 cases of the malignant group, papillomatous material sown in the wound presumably led to local recurrence. There was no operative mortality in the series. [2 other patients with bilateral renal papillomas are reported separately: Macalpine: *Brit. J. Surg.* 35: 137, Oct., 1947.]

[The author emphasizes the necessity of avoiding contamination of the wound by tumor cells. This is an important point, but one wonders about the validity of such statements as point (8) above, or "papillomatous material shed in an operation wound, whether the original growth appeared simple or malignant will invariably behave as a cancer," or "loss of a single papilloma cell in the connective tissue will almost certainly entail a malignant local recurrence." Nephro-ureterectomy with excision of the intramural ureter and adjacent bladder cuff is condemned as increasing the likelihood of tumor implantation in the wound and as being significantly more formidable surgically than juxtavesical nephro-ureterectomy with perurethral fulguration. The author admits, however, that the intramural ureter is a likely site of tumor development.]—*W. F. Whitmore, M.D.*

O'Heeron, Michael K. [Houston, Tex.]: Intrarenal lipoma: with report of an unusual case. *Urol. & Cutan. Rev.* 52: 73-76, Feb., 1948.

Ragins, Alex B., & Rolnick, Harry C.: Mucinous adenocarcinoma of the pelvis of the kidney. *Proc. Inst. Med. Chicago* 17: 45, Feb. 15, 1948.—Case report.

Sauer, Hans R. [Roswell Park Memorial Inst., Buffalo, N. Y.]: Wilms' tumors. *New York State J. Med.* 48: 497-501, Mar. 1, 1948.—Case report.

Scholl, A. J. [Los Angeles, Calif.]: Peripelvic lymphatic cysts of the kidney. Report of two cases. *J.A.M.A.* 136: 4-7, Jan. 3, 1948.

Stock, Francis E., & Wells, Charles: Primary carcinoma of the ureter. *Brit. J. Urol.* 20: 19-21, Mar., 1948.—Two case reports.

BLADDER AND URETHRA

Brayshaw, H. Currie: Papilloma of the bladder. *South African M. J.* 22: 263-266, Apr. 10, 1948.

Drew, J. Edwin [Cornell Univ. M. Coll., New York City]: Segmental resection of the bladder for cancer. *New York State J. Med.* 48: 877-878, Apr. 15, 1948.

Feves, Louis J., & Broun, James R. [Pendleton, Oreg.]: Primary carcinoma of the male urethra. Case report. *Northwest Med.* 47: 122, Feb., 1948.

Fulcher, Joseph [Tulsa, Okla.]: Leiomyosarcoma of the urinary bladder. *J. Oklahoma State M. A.* 41: 82-83, Mar., 1948.—Case report.

Huggins, Charles, & Johnson, Maxwell A. [Univ. Chicago, Sch. Med., Ill.]: Cancer of the bladder and prostate. *J.A.M.A.* 135: 1146-1152, Dec. 27, 1947.—In a study of 100 cases of bladder cancer, 2 classes were found: the papillary and the solid tumors. About 80% have a papillary component; a papillary tumor with a slender pedicle is usually cured while one with a wide base is often accompanied by infiltration. The upper half of the bladder was involved in 22%; the anterior bladder mucosa, 2%; the posterior inferior quadrant, 76%. Obstruction to emptying of the renal pelvis, with hydronephrosis, is frequently encountered. There were 77 males and 23 females, the highest age incidence between 55 and 65 yrs. Hematuria was the commonest symptom (94%) and an initial symptom in 76%. Diagnosis rests on cystoscopic examination. Neoplastic cells were found in the urine of 38. Biopsy can be made through the cystoscope. The present trend is toward treatment by surgery in most cases rather than by irradiation. Papillary tumors if small and few are treated by endoscopic fulguration with a Bugbee electrode; large, but with a narrow pedicle, by transurethral resection with a Stern-McCarthy resectoscope; those with a broad base are examined by an exploratory suprapubic cystotomy; and if apparently not infiltrating, the lesion is fulgurated with diathermy at open operation or excised by segmental resection, provided the tumor can be removed with a wide cuff of normal bladder tissue. Massive involvement of the bladder by small papillomas is treated by cystectomy. Unless metastasis or local infiltration is present, solid tumors are treated by cystectomy preceded by a deviation of the urinary stream, usually by bilateral ureterosigmoidostomy. The authors have abandoned the technique of implanting the ureter obliquely through the wall of the colon because this is conducive to postoperative ureteral stricture. Their own technique is briefly described. There were 4 hospital deaths following 136 operations on these 100 patients.

Cancer of the prostate is the cause of death of about 5% of white men more than 50 yrs. of age; the lesion is usually far advanced when the patient is first seen by a urologist. The tumor usually arises in the posterior region of the gland. Bone marrow and lymph nodes are the commonest locations for metastasis. Involvement of Virchow's supraclavicular node often occurs.

In 50 consecutive cases the local symptoms were increased urinary frequency (86%) and decreased size of the urinary stream (78%) which leads to acute urinary retention (28%); hematuria was uncommon (8%). The osseous metastases produced pain, usually sciatica or lumbar backache (56%), or pain in other regions where the bones are involved (14%). The onset of sciatica in a man over 40 yrs. demands a rectal examination. Involvement of the regional lymph nodes produces edema of the legs or genitalia (4%).

Diagnosis is made by rectal examination: the cancerous prostate is hard, nodular and lumpy, but nodular involvement is occasionally found in other conditions. Biopsy is occasionally necessary in small lesions. The perineal approach should be used so that radical perineal prostatectomy can be done if the diagnosis is confirmed. In these 50 cases there was x-ray evidence of osseous metastases in 31. Cystoscopic examination may reveal suggestive changes in some cases. Determination of serum acid and alkaline phosphatase is an important diagnostic procedure. The acid values are significantly elevated only in cancer of the prostate and only when metastasis (other than osteolytic only) has occurred. The alkaline phosphatase level may also be elevated, but this occurs in other diseases. In 100 cases of advanced prostatic cancer studied before treatment, one or both of the phosphatases were increased in 52%, both in normal range in 48%. When the serum acid phosphatase is greater than 10 units, it is certain that the patient has prostatic cancer with metastases; values between 5 and 10 units are presumptive of prostatic cancer, but are occasionally observed in other conditions. Early cancer of the prostate should be treated by total excision of the gland through a perineal approach. Unfortunately, most patients are too far advanced when first seen. In 138 consecutive cases of prostatic cancer seen by the authors, only 2 were considered sufficiently early for radical prostatectomy. Orchiectomy is recommended for inoperable cases. The results are not uniformly successful. Remission of varying lengths of time occurred in 18 of 20 with disseminated prostatic cancer treated by orchiectomy, while in 2 the disease was unmodified by the treatment. After 5 yrs. one patient was alive with slowly advancing carcinoma and 4 showed no clinical or laboratory evidence of cancer. These results have not been changed—6½ to 8 yrs. after orchiectomy. Chemical castration by estrogen treatment is indicated (1) when the patient refuses surgical castration, (2) in that small % of patients in whom the diagnosis is in doubt, and (3) in certain feeble men until the condition of the patient improves. It is customary to administer estrogen to those patients who have evidence of relapse or failure after orchiectomy. External irradiation has never been spectacularly successful in the treatment of prostatic cancer; it is capable of producing palliation and relief of pain in certain cases of osseous metastasis, and it is used in the treatment of appropriate patients in relapse.—C. A. Waltman, M.D.

Humphreys, Gustavus A. [N. Y. Hosp., Cornell Univ. M. Coll., New York City]: Ureterocutaneous anastomoses. *New York State J. Med.* 48: 879-882, Apr. 15, 1948.

Hutter, Karl: Ein weiterer Fall von Blasen-tumor nebst Bemerkungen über deren Strahlenempfindlichkeit. [Another case of bladder tumor, with notes on its x-ray sensitivity.] *Krebsarzt* 3: 67-68, Feb., 1948.—Scirrhous adenocarcinoma.

Jewett, Hugh J., & Cason, James F. [Johns Hopkins Hosp., Baltimore, Md.]: **Infiltrating carcinoma of the bladder: curability by segmental resection.** *South. M. J.* 41: 158-162, Feb., 1948.—In 55 cases of segmental resection, or partial cystectomy, for infiltrating carcinoma of the bladder, a correlation has been made between the survival of the patient after operation and the exact depth to which the tumor had penetrated the bladder wall, together with its histopathology. In 41 with infiltration more than half way through the muscularis, only 1 survived more than 5 yrs. In 14 with infiltration less than half way through the muscularis, there were no deaths from cancer of the bladder. 2 patients, who had had highly malignant tumors, are living 11 and 9 yrs. after operation. A third is living 8½ yrs., and a fourth, nearly 6 yrs. without recurrence. In the remaining 10, 5 yrs. have not yet elapsed since operation.—*Auth. Summ.*

Lumb, George [Westminster Hosp., London, Eng.]: **Surgical transplantation of a carcinoma of the urinary bladder.** *J. Path. & Bact.* 59: 682-683, Oct., 1947.—A case of carcinoma of the bladder is presented in which transplantation of the tumor occurred both to the posterior surface of the anterior abdominal wall and, later, to the skin of the abdominal scar.—*Auth. Summ.*

McLellan, A. M. [Cornell Univ. M. Coll., New York City]: **Transurethral treatment of bladder tumors.** *New York State J. Med.* 48: 876-877, Apr. 15, 1948.

Madison, Burle B. [Springfield, Ill.]: **Papillary carcinoma of a bladder diverticulum treated by transurethral resection.** *J. Urol.* 59: 42-43, Jan., 1948.

Marshall, Victor F. [Cornell Univ. M. Coll., New York City]: **Results of radiation therapy of bladder cancer.** *New York State J. Med.* 48: 875-876, Apr. 15, 1948.

Ratner, Max, & Schneiderman, Clarence [Jewish Gen. Hosp., Montreal, Que.]: **The relationship of urethral caruncle to carcinoma of urethra.** *Canadian M. A. J.* 58: 373-376, Apr., 1948.—Case report.

Reid, Wells C.; Westcott, G. W., & Summers, John E. [Goodrich Gen. Hosp., Goodrich, Mich.]: **Carcinoma in exstrophy of the bladder.** *Am. J. Surg.* 75: 601-606, Apr., 1948.—Case report.

Schnittman, Morris [Cornell Univ. M. Coll., New York City]: **Results of the ureterointestinal anastomoses.** *New York State J. Med.* 48: 882-884, Apr. 15, 1948.

Seng, Magnus, & Siminovitch, Moses [Roy. Victoria Hosp., Montreal, Que.]: **Carcinoma of the urethra in the female.** *Canadian M. A. J.* 58: 29-33, Jan., 1948.—Six case reports and review of the literature.

Shackman, Ralph [Brit. Post-Grad. M. Sch., London, Eng.]: **The treatment of bladder can-**

cer. *Brit. J. Surg.* 35: 140-146, Oct., 1947.—The early history and treatment of bladder tumors are reviewed. 76 cases were seen at the British Post-Graduate Medical School from 1935 to 1946. Of this number, 19 refused or were not advised surgical treatment; 27 were given palliative treatment only; 30 had either complete cystectomy after ureterocolic anastomosis or partial cystectomy. In 21 in whom cystectomy and ureterocolic anastomosis were done, there were 12 postoperative deaths (57%); none, in 9 having partial cystectomy. Of 9 surviving total cystectomy and ureterocolic transplantation, 4 were dead within 30 mos. and 5 living from 3 to 48 mos. Of 9 having partial cystectomy, 5 developed recurrence in 3 to 54 mos. The remaining 4 were well for 1 to 32 mos. but were not seen thereafter. Of the whole series of 76 patients, only 16 were known to have survived for longer than 6 mos. from the time of the first visit, and 44 were known to be dead within 6 mos.

Possible alternative surgical methods of treatment are: cystectomy and cutaneous ureterostomy as a preliminary to ureterocolic and ureterocolic implantation; bilateral nephrostomy as a preliminary to ureterocolic anastomosis; transverse colostomy with complete division of the bowel and closure of the proximal cut end of the distal loop preliminary to ureterocolic anastomosis; extraperitoneal ureterocolic anastomosis. The use of x-rays and Ra as alternative methods of treatment is discussed. In 55 patients so analyzed, 6 had clinical evidence of metastases, 14 had metastases at autopsy, 16 had no metastases at operation (but 4 developed them later), and 19 had no metastases at autopsy. Obstruction of one or both ureters was present in 37 of 62 patients investigated by excretion urography, operation, or autopsy. Earlier diagnosis, reduction of operative mortality, and planned dissection of the iliac lymph nodes at the time of ureterocolic anastomosis and cystectomy are cited as future hopes in the therapy of bladder cancer.

[The author's presentation of total experience with bladder cancer is commendable and its general adoption by authors on this subject would do much to clarify the value of various methods of treatment of the disease. The operative mortality in the author's series of ureterointestinal anastomoses and cystectomies is prohibitive; and, although comparable to that of Hinman and Smith (1939) and Walker-Taylor (1931) it is far higher than that recently reported from various clinics in this country. The suggestions for alternative methods of operative treatment, although surgically feasible, seem born primarily of desperation attendant on the high operative mortality obtained. Unfortunately, no detailed description of operative technique is given nor is the preoperative condition of the patient indicated. The late results of treatment by ureterointestinal anastomosis and cystectomy cannot yet be evaluated.]—*W. F. Whitmore, M.D.*

Sirsat, M. V. [Tata Memorial Hosp., Bombay, India]: **Epithelial tumours of the urinary**

bladder. *Indian J. M. Sc.* 1: 269-274, Dec., 1947.—A review of 30 tumors.

Vnllett, Brice S. [Del. Hosp., Wilmington]: Perineal and vaginal total cystectomy. *Delaware State M. J.* 20: 6-7, Jan., 1948.

Whitmore, Willet F., Jr., & Benli, Neil P. [Cornell Univ. M. Coll., New York City]: Total cystectomy. *New York State J. Med.* 48: 884-886, Apr. 15, 1948.

PROSTATE AND SEMINAL VESICLE

Beatty, Ralph P. [Uniontown, Pa.]: Life expectancy in cancer of the prostate. *Pennsylvania M. J.* 51: 419-422, Jan., 1948.

Bensley, E. H.; Wood, Phyllis; Mitchell, Sallie, & Milnes, Betty [Montreal Gen. Hosp., Montreal, Que.]: Estimation of serum acid phosphatase in the diagnosis of metastasizing carcinoma of the prostate. *Canadian M. A. J.* 58: 261-264, Mar., 1948.

Birdsall, Joseph C.: Carcinoma of the prostate with an evaluation of its present day management. *J. Urol.* 59: 220-228, Feb., 1948. Also in part in *Philadelphia Med.* 43: 197, 199, Sept. 27, 1947.

Cassuto, Auguste [École Med. Rome, Italy]: Sur le traitement médico-chirurgical du cancer de la prostate. Orchiectomie souscapsulaire et hormonothérapie. [Medicosurgical treatment of cancer of the prostate. Subcapsular orchiectomy and hormone therapy.] *J. d'uro.* 53 (10/11): 423-430, 1946/47.

Deming, Clyde L., & Hovenaninn, Michael S. [Yale Univ. Sch. Med., New Haven, Conn.]: The hormonal factor in heterologous growths of human prostatic cancer. *J. Urol.* 59: 215-219, Feb., 1948.—Heterologous transplantation of human prostatic adenocarcinoma to the anterior chamber of the guinea-pig eye was done successfully in 43.6% of 94 males and 11.3% of 28 females. The cellular morphology of the parent human tumor was maintained unchanged through 10 generations. In the first 2 generations, about 75% of the males grew cancer tissue; none of the females grew transplanted prostatic cancer in the first 5 generations, suggesting that androgen was necessary for its growth. In the 6th generation, 1 female given androgen was successfully inoculated. In the 8th generation, 50% of both males and females grew tumors; as these females were untreated, this suggests that the tumor had become feminized and independent of both male and female hormones. None in which the tumor completely filled the anterior chamber of the eye developed any increase in the blood-serum acid phosphatase, nor did heterologous tumors of the 4th and 6th generations take the lead stain for the enzyme. In the 10th generation about 40% of both sexes grew tumors, emphasizing again that the tumor probably was little influenced by male and female hormones. The observations are correlated with the clinical behavior

of prostatic cancer and some inferences drawn regarding improvement of therapy. The authors recommend early treatment of inoperable cases of prostatic cancer by castration and large doses of estrogen.

[The authors employ a most promising method for the investigation of prostatic cancer. Their series of animals is small, inadequately controlled, and incompletely explained but the method represents a start in this fertile field. A clinical trial of their suggestions for therapy certainly seems warranted.]—*W. P. Whitmore, M.D.*

Gilbert, George G. [Asheville, N. C.]: The cellular changes in carcinoma of the prostate following hormonal therapy. *North Carolina M. J.* 9: 18-21, Jan., 1948.

Henline, Roy B. [New York City]: Prostatic disease: with special reference to early diagnosis and treatment of carcinoma of the prostate. *Nebraska M. J.* 33: 84-88, Mar., 1948. Also in *New York Med.* 3: 17, Nov. 5, 1947.

Hovenaninn, Michael S., & Deming, Clyde L. [Yale Univ. Sch. Med., New Haven, Conn.]: The heterologous growth of cancer of the human prostate. *Surg., Gynec. & Obst.* 86: 29-35, Jan., 1948.—Cancer of the prostate gland has been successfully transplanted heterologously in guinea pigs for the first time, demonstrating the autonomous nature of this cancer. Serial transplantation shows that prostatic cancer is under the influence of endocrine factors. When transplanted heterologously in male castrated guinea pigs, human cancer of the prostate did not grow. Similarly, in human clinical observation, cancer of the prostate has not been found in eunuchs. Stimulation of female guinea pigs with small amounts of androgen did not affect the growth of transplanted prostatic tumor but stimulation of a female with massive doses aided in establishing a successful take of prostatic cancer. Carcinoma of the human prostate heterologously transplanted in guinea pigs lost a fundamental biological activity, the production of the enzyme, acid phosphatase. This fact was demonstrated by the absence of elevation of blood-phosphatase level in tumor-bearing animals and absence of stain for phosphatase in sections of tissue removed from the guinea-pig eye. Heterologous transplantation of human prostatic cancer has indicated that the cellular nucleus holds the key to the biological activity of malignant cells which have become autonomous, disordered in growth, and uncontrollable in cellular metabolism.—*Auth. Summ.*

McCaffery, Robert, & Hess, Elmer [St. Vincent's Hosp., Erie, Pa.]: The treatment of prostatic carcinoma. *J. Internat. Coll. Surgeons* 11: 68-71, Jan./Feb., 1948.—Analysis of 197 cases.

McCrea, Lowrain E. [Philadelphia, Pa.]: Primary carcinoma of the seminal vesicles. Differentiation from extrarectal and rectal carcinoma and comparative study. *J.A.M.A.* 136: 679-682, Mar. 6, 1948.—Case report and review of literature.

Semans, James H. [Atlanta, Ga.]: Early carcinoma of the prostate: its diagnosis and treatment. *South. Surgeon* 14: 273-277, Apr., 1948.—Survey of the literature and case report.

Sinclair, A. B., & Fitzpatrick E. J. [Montreal Gen. Hosp., Que.]: Anaplastic carcinoma of the seminal vesicles with extensive invasion of the bladder wall. *Canadian M. A. J.* 58: 386-388, Apr., 1948.—Case report.

Smith, George Gilbert [Mass. Gen. Hosp., Boston]: Carcinoma of the prostate. *Bull. New England M. Center* 10: 63-70, Apr., 1948.

Tecvens, W. P. [Wawota, Sask.]: Relief of septicemia in carcinoma of the prostate by procaine. *Canadian M. A. J.* 58: 384, Apr., 1948.—Case report.

Thompson, Raymond [Charlotte Memorial Hosp., N. C.]: Carcinoma of the prostate. *South. Med. & Surg.* 110: 33-35, Feb., 1948.

Toulson, W. Houston, & Hawkins, Charles W. [Sch. Med., Univ. Md., Baltimore]: Paraplegia as the result of metastasis from carcinoma of the prostate gland. *Bull. Sch. Med. Univ. Maryland* 32: 159-162, Jan., 1948.—Case report.

TESTIS AND SCROTUM

Ahlbom, Hugo [Radiumhemmet, Stockholm, Sweden]: Malignant tumours of the testis. Treatment at Radiumhemmet, Stockholm. *Acta radiol.* 28: 669-680, Nov., 1947.—From 1922 to 1941 incl. 119 patients with malignant tumors of the testis were treated. The results [alive and well] after 5 yrs. for the whole series was about 50%, in cases without metastases about 70%. The result [alive and well] after 5 yrs. was about 65% for the seminomas (65 cases) and about 35% for the adenocarcinomas and malignant mixed tumors (44 cases). The seminomas without metastases [on admission] showed a 5-yr.-curc rate of about 80%. Orchiectomy and postoperative x-ray treatment [2400 r], chiefly on the para-aortic lymph nodes, is considered the best method. Practically no information regarding the prognosis was obtained from prolan tests made in 59 cases. Blood sedimentation tests seem to be of particular prognostic value in this tumor group [good if rate remains normal for 2-3 yrs. after orchiectomy; if rate rises later, metastases probable; when metastases present, usually exceeded 25-30 mm./hr.] —*Auth. Summ.*

Rogers, Herbert [Hillingdon Co. Hosp., Eng.]: Large intrascrotal myxofibroma. *Brit. J. Surg.* 35: 323-324, Jan., 1948.—Case report.

HEMATOPOIETIC SYSTEM

Ardashnikov, S. N. [Molotov's Cent. Res. Inst. Roent. & Radiol., Russia]: "Lymphatic reactions" among relatives of leukaemic patients. *Brit. M. J.* 2: 955-958, Dec. 13, 1947.—The author reports 3 cases showing a peculiar

ability of the lymphatic system in several relatives of leukemic patients, consisting of an increase in the percentage of lymphocytes following febrile illnesses. In 1, a sister had died of leukemia, type undetermined, some 33 yrs. before. When the lymphatic reaction was found in the other 2 (identical twins), the maternal grandfather was suffering from chronic lymphatic leukemia. In the first case, differential white-cell counts showed lymphocytes up to 95%; in the twins, to 93% and 64.5%. The total leukocyte counts ranged between 4400 and 24,000. [There is no report of heterophile agglutinations being done in any of these cases.] The author believes these lymphatic reactions may be an expression of the leukemia gene.—*J. H. Burchenal, M.D.*

Bedinger, Paul L.; Poncher, Henry G., & Limarzi, Louis R. [Chicago, Ill.]: Effect of urethane on leucemia. *J. Lab. & Clin. Med.* 32: 1394-1395, Nov., 1947.

Berman, Lawrence; Axelrod, Arnold R.; Sharp, E. A., & Vonder Heide, E. C. [Detroit, Mich.]: Experiences with urethane in eight patients with malignant disease. *J. Lab. & Clin. Med.* 32: 1431-1432, Nov., 1947.

Bichel, J. [Univ. Aarhus, Den.]: Effect of *p*-aminobenzoic acid on the leucocyte count in leukaemia. *Nature* 161: 353, Mar. 6, 1948.—The author treated 2 cases of chronic myeloid, and 4 cases of chronic lymphatic, leukemia with *p*-aminobenzoic acid in the doses of 2 gm. every 2 hrs. as recommended in rickettsial infections. This dosage was later decreased with no change in effect. In all 6, the administration was accompanied by an abrupt rise in leukocyte count with daily increases of 10,000 to 100,000 white blood cells accompanied in 4 to 5 days by soreness in the enlarged nodes and spleen. A slight shift to the left was seen in the peripheral blood and bone marrow of the patients with chronic myeloid leukemia. *p*-aminobenzoic acid was given to 8 patients with normal blood pictures without causing significant variations.—*J. H. Burchenal, M.D.*

Brunsting, Louis A. [Mayo Clin., Rochester, Minn.]: Recent advances in dermatology and syphilology. *Canadian M. A. J.* 58: 133-137, Feb., 1948.—Nitrogen mustard in mycosis fungoides is discussed briefly.

Coles, William C., & Schulz, Milford D. [Mass. Gen. Hosp., Boston]: Bone involvement in malignant lymphoma. *Radiology* 50: 458-462, Apr., 1948.—Of 288 cases of malignant lymphoma of all varieties seen during the 10-yr. period [Jan., 1936 to Dec., 1945] 13% were found to involve bone. The spine was the most common site. With the exception of solitary reticulum-cell sarcoma of bone, which may be a curable disease, the appearance of bone involvement seems to have no notable effect upon the prospect for survival of an individual beyond that which is well recognized for the various subgroups of the disease. Neither does the time of the appearance of the bone lesion, whether

early or late in the course of the disease, affect appreciably the ultimate prognosis, except in widespread reticulum-cell sarcoma, when it tends to occur terminally. Giant follicular lymphoma was found to involve the skeletal system in a disproportionately low degree; reticulum-cell sarcoma in a relatively high degree. No significant age or sex predilection for bone involvement in malignant lymphoma was found.—*Auth. Summ.*

Cook, Thomas J. [Miami, Fla.]: Leuremin. Report of a case. *Oral Surg., Oral Med. & Oral Path.* 1: 231-232, Mar., 1948.—Oral manifestations.

Craver, Lloyd F. [Memorial Hosp., New York City]: Lymphomas and leukemias. The value of early diagnosis and treatment. *J.A.M.A.* 136: 244-249, Jan. 24, 1948.—Survey of results, early signs, prevention, and methods of treatment.—*D. A. S.*

Craver, Lloyd F. [Memorial Hosp., New York City]: The nitrogen mustards: clinical use. *Radiology* 50: 486-493, Apr., 1948.—A chronologic summary is given of the history, the pertinent literature, method of use, dosage, toxicity, and results in the clinical application of the nitrogen mustards to diseases of the lymphatic system in more than 300 cases at the Memorial Hospital. These included: 102 Hodgkin's disease; 66 lymphosarcoma; 65 leukemia (17 acute, 1 monocytic, 17 chronic lymphatic, 30 chronic myeloid); 33 bronchogenic cancer; 15 miscellaneous cancers; 16 various sarcomas. In no case did "cure" result. Marked palliation was noted in certain types. In generalized Hodgkin's disease with constitutional symptoms rapid detoxification of the patient occurred. When lymphosarcomatous lesions were immediate threats to life (as in mechanical obstructions) and surgery or radiation was not feasible, these agents were useful. Nitrogen mustard was effective in allaying symptoms in anaplastic lung cancers. The agents offer doubtful, if any, advantage over x-ray therapy in early or intermediate Hodgkin's disease, in most cases of lymphosarcoma, or chronic leukemia. It is hoped that a congener may be found that will be less toxic and more effective in a greater number of cancers.—*H. D. Diamond, M.D.*

Craver, Lloyd F. [Memorial Hosp., New York City]: Recent advances in treatment of lymphomas, leukemias and allied disorders. The Bulkley Lecture. *Bull. New York Acad. Med.* 24: 3-25, Jan., 1948.

Dubin, I. N. [Univ. Tenn. Coll. Med., Memphis]: The poverty of the immunological mechanism in patients with Hodgkin's disease. *Ann. Int. Med.* 27: 898-913, Dec., 1947.—By reviewing the literature and 262 case records of patients with Hodgkin's disease, the author is impressed that in this disease there is a deficiency in the immunological response. This view is supported by the following observations on patients with Hodgkin's disease: anergy to

tuberculin; a decreased incidence of positive Wassermann reactions among colored patients (16.7% positive as compared with an expected 30% in the population); negative typhoid (41 cases) and paratyphoid A and B (32 cases) agglutination tests; one patient who failed to develop "II" and "O" agglutinins to a course of typhoid vaccine; 51 of 52 patients with negative *Brucella* agglutination tests; and a number of negative miscellaneous immunological tests.

The author does not believe that this deficiency of antibody response is due to a general interference with plasma-protein formation. He considers the possibility that Hodgkin's cells are unable to phagocytose particles or fabricate antibodies, but data are inadequate to support this. It is generally thought that the deficiency in antibody response is due to the replacement of this reticulo-endothelial system by the immunologically inactive Hodgkin's cells. The alternative hypothesis is suggested that Hodgkin's disease is a primary metabolic dysfunction interfering with the mechanism of antibody formation. The dysfunctioning reticulo-endothelial cells undergo hyperplasia and hypertrophy in a fruitless endeavor to overcome the deficiency. On this basis it is suggested that besides conventional treatment, substances stimulating the immunological mechanisms be used, and it is considered possible that pyridoxine may be of importance.—*D. A. Karnofsky, M.D.*

Friedman, Ruben, & Stritzler, Conrad [Temple Univ. Sch. Med., Philadelphia, Pa.]: Mycosis fungoides resisting treatment with both nitrogen mustard and anti-reticular cytotoxic serum. *J. Invest. Dermat.* 10: 227-228, Apr., 1948.—Case report.

Garb, John [N. Y. Post-Grad. M. Sch. & Hosp., New York City]: Mycosis fungoides (granuloma fungoides), tumor stage, responding rapidly to antimony preparations. Preliminary report. *J. Invest. Dermat.* 10: 43-49, Feb., 1948.—A woman aged 49 with lesions of mycosis fungoides in the tumor stage was treated since April 28, 1947 [i.e., for 7 mos.] with 10 intravenous injections of tartar emetic, followed by 32 intramuscular injections of "Stibanose." The patient showed a rapid and striking response noticeable within 3 wks. Only a few residual lesions are now seen and these are steadily undergoing involution.—*Auth. Summ.*

Gould, W. R. [Aberdeen Roy. Infirmary, Scotland]: Acute lymphatic leukaemia presenting with skin lesions and mastoiditis. *Brit. M. J.* 1: 150, Jan. 24, 1948.

Haden, Russell L. [Cleveland, Ohio]: Blood dyscrasias and lymphoblastomas. *Kentucky M. J.* 46: 138-142, Apr., 1948.

Hamann, Anna [Dept. Med., Univ. Chicago, Ill.]: External irradiation with roentgen rays and radium in the treatment of human leukemias, lymphomas, and allied disorders of the hemopoietic system. *Radiology* 50: 378-386, Mar., 1948.—Results in 337 cases.

- Hare, Hugh F.; Mulry, William C., & Sornberger, C. Franklin [Lahey Clin., Boston, Mass.]: Lymphoid tumors. *Radiology* 50: 506-514, Apr., 1948.—Early diagnosis and treatment of lymphoid tumors constitute the only approach to a successful outcome in this disease. Our efforts should be bent toward this end, namely, to establish the diagnosis of the disease while it is still localized and then to deliver an obliterative dose of radiation treatment. The lethal tumor dose in most instances can be fairly adequately attained by giving 2400 r to the tumor. 50 (29%) of 181 patients were living and well at the end of a 5-yr. period, and of the 21 patients followed for a 10-yr. period, 17 remained alive and well.—*Auth. Summ.*
- Hettig, Robert A. [Houston, Tex.]: Result of methyl-bis (beta-chloroethyl) amine hydrochloride therapy: a preliminary report of a nitrogen mustard. *J. Lab. & Clin. Med.* 32: 1431, Nov., 1947.
- Hirschboeck, John S.; Lindert, M. C. F.; Chase, Jules, & Calvy, Thomas L. [Marquette Univ. Sch. Med., Milwaukee, Wis.]: Effects of urethane in the treatment of leukemia and metastatic malignant tumors. *J.A.M.A.* 136: 90-95, Jan. 10, 1948.—Urethane was used in 25 cases of leukemia and lymphomatous diseases and 8 miscellaneous cancers (4 carcinomas of the stomach with metastasis; 1 each—malignant melanoma, rectal carcinoma, retroperitoneal myosarcoma, lymphoepithelioma). Using 0.5 gm. gelatine or enteric-coated capsules, the usual dosage was 1.0 gm. t.i.d., although occasionally 2.0 gm. t.i.d. was given. As much as 2.0 gm. of a 50% solution was given intramuscularly without any complaints of local irritation. Oral administration gave satisfactory remissions in 4 cases of chronic myelogenous leukemia. 9 patients with chronic lymphatic leukemia showed a variable response: good remissions occurred in 2; some improvement, in 4; the remaining 3 died. Severe leukopenia occurred in most of the 9 cases of acute and subacute leukemia without any substantial influence on the course of the disease. No clinical improvement was noted in the 8 cancer cases treated with urethane.
- The authors conclude that the place for urethane in the treatment of leukemia cannot be designated precisely now. The drug appears to be of little or no benefit in producing remissions or prolonging life in acute leukemia. Its action in chronic lymphatic leukemia is variable but when effective, produces results comparable to x-ray therapy. It is most consistently successful in controlling the clinical and hematologic abnormalities in chronic myelogenous leukemia. They believe its action is less precise and has no advantage over x-rays other than its ease of administration.—*J. H. Burchenal, M.D.*
- Hirvonen, Martti [Hämeenlinna District Hosp., Fin.]: Observations on the treatment of leukemia with uretan [sic]. *Ann. med. int. Fenniae* 36 (3): 508-515, 1947.—Two case reports.
- Holowach, Jean [Wash. Univ. Sch. Med., St. Louis, Mo.]: Chronic lymphoid leucemia in children. *J. Pediat.* 32: 84-86, Jan., 1948.—A review.
- Jackson, Henry, Jr. [Harvard M. Sch., Boston, Mass.]: The practical aspects of the diagnosis, treatment, and prognosis of Hodgkin's disease and allied disorders. *Radiology* 50: 481-485, Apr., 1948.
- Krebs, Carl, & Bichel, Jorgen [Municipal Hosp., Aarhus, Den.]: Results of roentgen treatment in chronic myelogenous leukosis. *Acta radiol.* 28: 697-704, Nov., 1947.
- Lang, V. F.; Morton, S. A.; Steele, J. D., & Schaeffer, A. A. [Milwaukee, Wis.]: Cyst of the spleen. Case report. *Ann. Surg.* 127: 572-576, Mar., 1948.—A case of an epidermoid cyst of the spleen with symptoms of thoracic origin is reported. Splenectomy was performed through a transthoracic approach. We have found no similar case reported in the literature.—*Auth. Summ.*
- Lawrence, John H.; Dobson, R. Lowry; Lowbeer, V. A., & Brown, Bruce R. [Univ. Calif., Berkeley]: Chronic myelogenous leukemia. A study of 129 cases in which treatment was with radioactive phosphorus. *J.A.M.A.* 136: 672-677, Mar. 6, 1948.—Comfortable life was prolonged in 129 patients with chronic myelogenous leukemia treated with P^{32} alone or combined with x-rays. The somewhat selective irradiation provided by P^{32} has not resulted in any marked improvement in the duration of life in this disease. It is a convenient method to give generalized irradiation, with the added advantage of absence of radiation sickness. The fact that 33 patients in this series have lived or are living 5 or more yrs. after the onset of symptoms is a reminder that many patients with chronic leukemia have many yrs. of relatively comfortable life, and it is not possible to predict which these will be when they are first seen. Although these studies indicate that P^{32} may be the best therapeutic agent in the treatment of chronic myelogenous leukemia, they also add further emphasis to the need for a search for methods other than irradiation for the ultimate control of this baffling disease.—*Auth. Summ.*
- Louis-Bar, Denise [Liège, Belg.]: Sur les manifestations cérébrales de la lymphogranulomatose maligne et le problème de l'encéphalite lymphogranulomateuse. [Cerebral symptoms of malignant lymphogranulomatosis (Hodgkin's disease) and the problem of lymphogranulomatous encephalitis.] *J. belge de neurol. et de psychiat.* 47: 703-728, Dec., 1947.—Case report and review.
- McDonald, John B., & Hamrick, Jewell G. [W. E. Branch Clin., & Hollywood Presbyterian Hosp., Los Angeles, Calif.]: Acute megakaryocytic leukemia. *Arch. Int. Med.* 81: 73-84, Jan., 1948.—Case report and review of literature.
- Matveyenko, Olga [Regina Grey Nuns' Hosp.,

- Sask.]: Monocytic leukaemia. A report of three cases. Canadian J. M. Technol. 10: 21-25, Mar., 1948.
- Melton, G., & Montuschi, E.: Polycythaemia vera. Hypertensive heart disease. Erythromelalgia syndrome and osteoarthropathy in the right leg. Proc. Roy. Soc. Med. 41: 101-102, Feb., 1948.—Case report.
- Munshi, C. P. [K. E. M. Hosp., Bombay, India]: Chloroma. Indian Physician 6: 283-284, Dec., 1947.
- Osgood, Edwin E. [Univ. Oreg. M. Sch., Portland]: Differential diagnosis and treatment of the leukemias. Northwest Med. 47: 181-185, Mar.; 257-260, Apr., 1948.
- Post, Charles F., & Lincoln, Charles S. [Coll. Phys. & Surgeons, Columbia Univ., New York City]: Mycosis fungoides. Report of two unusual cases with autopsy findings. J. Invest. Dermat. 10: 135-153, Mar., 1948.
- Rielman, Samuel [Veterans Adm. Hosp., Richmond, Va.]: Roentgen manifestations in Hodgkin's disease of retroperitoneal lymph nodes. Radiology 50: 521-525, Apr., 1948.—Case report.
- Rocchietta, Sergio: Isolamento di sostanze caratteristiche dalle urine di leucemici. [Isolation of characteristic substances in the urine of leukemias.] Minerva med. 2: 267, Sept. 22, 1947.—A review.
- Rosenthal, Eugene [Budapest, Hung.]: Nitrogen-mustard therapy combined with splenectomy. Lancet 1: 408, Mar. 13, 1948.—Preliminary report of 4 cases.
- Roulet, Fred. [Univ. Basel, Swt.]: Das Verhalten der Milz beim Retothelsarkom der Lymphknoten. [Behavior of the spleen in reticulosarcoma of the lymph nodes.] Schweiz. Ztschr. Path. u. Bakt. 10 (suppl.): 88-101, 1947.
- Scott, Leonard G. [Bridgeton, N. J.]: Leukemia-like reaction to one dose of sulfadiazine. J. M. Soc. New Jersey 45: 115, Mar., 1948.—Case report.
- Sherry, Milton [Sinai Hosp., Baltimore, Md.]: Nitrogen mustards in the treatment of Hodgkin's disease and lymphosarcoma. South. M. J. 41: 118-129, Feb., 1948.—War-gas research in World War II gave genesis to our knowledge of the nitrogen mustards. The actions of this group of agents are not comparable to any other chemical agent, but yet mimic action of x-rays on cells. Mention is made of the manner of procurement, preparation, and method of administration of this group of agents. 11 patients were treated with HN₂ (methyl-bis [β -chloroethyl] amine hydrochloride); of these, 6 had Hodgkin's disease, 2 lymphosarcoma, 1 giant-follicle lymphoma, and 2 melanocarcinoma. Hodgkin's disease responded best: giant-follicle lymphoma, only fair; and the others failed to respond. Criteria of response were: lymph-node regression, shrinkage of spleen and liver, abatement of fever, and clearance of pleural effusion and improvement in pulmonary parenchymal manifestations of disease. The well-established toxic effects of these agents on the hematopoietic system, the gastrointestinal tract, and vein walls are discussed. Lymph-node studies before and after treatment showed no microscopic change in the 2 cases so studied.—H. D. Diamond, M.D.
- Siddons, William H. [Univ. Ark. Sch. Med., Little Rock], & Wells, Benjamin B.: Nitrogen mustard treatment in chronic myelogenous leukemia. J. Arkansas M. Soc. 44: 203-206, Feb., 1948.
- Spurr, Charles L.; Smith, Taylor R., & Jacobson, Leon O. [Dept. Med., Univ. Chicago, Ill.]: Chemotherapy in human lymphomas, leukemias, and allied disorders of the hematopoietic system. Radiology 50: 387-394, Mar., 1948.—Survey of literature and report of 3 cases.
- Symmers, Douglas [Bellevue Hosp., New York City]: Lymphoid diseases. Hodgkin's granuloma, giant follicular lymphadenopathy, lymphoid leukemia, lymphosarcoma and gastrointestinal pseudoleukemia. Arch. Path. 45: 73-131, Jan., 1948.—The author presents a most comprehensive report of the diseases of the lymphoid system; a monograph rather than a review. The paper is an intricate, detailed résumé of the history, etiology, eponymology, pathogenesis, diagnosis, and treatment of the lymphoid diseases. Symmers relates his experiences with these maladies as he has seen them at the autopsy table at the Bellevue Hospital. He believes that Hodgkin's disease is a process of myeloidization of hyperplastic lymph nodes, possibly due to a virus; evidence is presented for this view. He propounds that giant follicular lymphadenopathy is a toxic inflammatory disease capable of sarcomatous transformation. Parallels are drawn between Hodgkin's disease and giant follicular lymphadenopathy. Symmers' conceptions of the etiology and pathogenesis of lymphosarcoma and lymphoid leukemia as well as his experiences with these diseases are put in clear, lucid, easily read language. The paper contains much of fact, much of interest, and much of experience with the lymphoid diseases—all related in monographic proportions, yet easy to assimilate.—H. D. Diamond, M.D.
- Van Wien, Stefan [Northwest. Univ. M. Sch., Chicago, Ill.]: Lymphocytoma of the orbit successfully treated by roentgen irradiation. Report of a case. Am. J. Ophth. 31: 209-212, Feb., 1948.
- Weisberger, Austin S., & Heinle, Robert W. [Lakeside Hosp. & Sch. Med., West. Reserve Univ., Cleveland, Ohio]: Study of fixed tissue sections of sternal bone marrow obtained by needle aspiration. I. Method and the morphology in various conditions. II. Comparison of nucleated cell count and volumetric pattern with histologic appearance. Am. J. M. Sc. 215: 170-176; 177-181, Feb., 1948.

Wilson, Sloan J.; Wise, George W., Jr.; Campbell, James W., & Coxsey, La Vonne [Univ. Kansas Sch. Med., Kansas City]: The treatment of leukemia and allied disorders with urethane (ethyl carbamate). *J. Kansas M. Soc.* 49: 97-100, Mar., 1948.

MUSCULOCUTANEOUS SYSTEM

Björkroth, Torsten [County Hosp., Kristinehamn, Sweden]: A case of Abrikossoff's tumor or so-called myeloblastic [sic] myoma. *Acta chir. Scandinav.* 3: 251-256, Dec. 5, 1947.

Cappell, D. F. [Univ. Glasgow, Scotland]: Tumours of striated muscle. Post-graduate lecture delivered at the Royal College of Surgeons of England, on 9th September, 1947. *Ann. Roy. Coll. Surgcons England* 2: 80-92, Feb., 1948.

Harris, V. C. J. [West Cumberland Infirmary, Whitehaven, Eng.]: Three cases of synoviomia. *Brit. M. J.* 1: 447-448, Mar. 6, 1948.

Kammerer, E. [Univ. Innsbruck, Austria]: Über ein metastasierendes malignes Rhabdomyom des linken M. psoas. [A metastatic malignant rhabdomyoma of the left psoas muscle.] *Krebsarzt* 3: 60-67, Feb., 1948.—Case report.

Slaughter, Danely P. [Univ. Ill. Coll. Med., Chicago, Ill.]: Superficial tumors of the head and neck area. *S. Clin. North America* 28: 69-81, Feb., 1948.

Stout, Arthur Purdy [Coll. Phys. & Surgeons, Columbia Univ., New York City]: Mesenchymoma, the mixed tumor of mesenchymal derivatives. *Ann. Surg.* 127: 278-290, Feb., 1948.—Eight cases of malignant tumors of 2 or more cell types composed of cells of mesenchymal derivation are reported. The author proposes the name, "mesenchymoma" for such tumors, and regards them as dysontogenetic growths. Similar tumors, seen occasionally in the breast or urogenital tract, are usually called mixed mesodermal tumors. Only 1 of the author's cases occurred in either region. 2 arose in the muscles of the lower extremity and 1 in each of the following: subcutaneous tissue of the leg, gluteal muscles, liver, pleura, and anterolateral neck region. The multiplicity of cell types was illustrated by 1 case which showed foci of leiomyosarcoma, osteogenic sarcoma, chondrosarcoma, reticulum-cell sarcoma, and hemangioma. Another showed areas of fibrosarcoma, myxoma, liposarcoma, hemangiopericytoma, and hemangioendothelioma. A third contained 4 distinct types of sarcoma. 2 were characterized by 3 cell types, and 3 cases revealed 2 malignant mesenchymal elements in each. The group comprised 6 males, 2 females, aged 6 to 77 yrs. The course of 5 patients is given: 1 died 12 yrs. after the appearance of a tumor in the thigh; before death a bronchoscopic biopsy disclosed a reticulum-cell sarcoma believed to be metastatic from the thigh tumor. Another had 3 local recurrences and died $2\frac{1}{2}$ yrs. after

the initial appearance of a tumor in the buttocks. A third died 11 mos. after a tumor of the thigh was noted and 7 mos. after local excision of the mass. Resection of a neck tumor and radiation therapy were followed by $9\frac{1}{2}$ mos. freedom from local recurrence in 1. No evidence of recurrence was noted in a patient 2 yrs. after excision of a tumor in the liver. The author believes that early and radical excision, amputation if necessary, is the obvious treatment.—*P. J. Fitzgerald, M.D.*

SKIN

Alexander, Robert Julian [Salt Lake City, Utah]: Two case reports. *Plast. & Reconstruct. Surg.* 3: 60-65, Jan., 1948.—Case 2: epidermoid carcinoma of knee, Marjolin's ulcer.

Allen, Arthur C. [Memorial Hospital, New York City]: Persistent "insect bites" (dermal eosinophilic granulomas) simulating lymphoblastomas, histiocytoses, and squamous cell carcinomas. *Am. J. Path.* 24: 367-387, Mar., 1948.—Reactions to insect bites may provoke such marked epidermal hyperplasia as to simulate a squamous carcinoma, or they may lead to a dense dermal infiltrate that may easily be mistaken for mycosis fungoides, Hodgkin's disease, or other lymphoma. This simulation is enhanced by the persistence of the local reaction to insect bites in some instances for over 2 yrs. The occurrence of numerous plasma cells and hydropically vacuolated histiocytes in addition to the abundant eosinophilic leukocytes suggests the diagnosis of insect bites. The presence of an epidermoid inclusion cyst is further evidence. The association of this type of dermal infiltrate with conspicuous overlying pseudoepitheliomatous hyperplasia is strongly presumptive of the reaction to an insect bite.—*Auth. Abst.*

Bang, Kamma [Finsen M. Light Inst., Copenhagen, Den.]: Two cases of angiokeratoma corporis circumscriptum. *Acta dermat-venereol.* 27 (5): 346-351, 1947.—It is suggested the hydradenoma vulvae originated as a disturbance in development of the primordium of the hair follicle, sebaceous gland, and apocrine sweat gland.—*M. C. J.*

Cantor, Hyman [M. Coll. Va., Richmond]: Cancer following burn scars. *Virginia M. Monthly* 75: 197-199, Apr., 1948.

Clark, Philip J., & Johnson, Thomas M. [Univ. Kansas Sch. Med., Kansas City]: Epidermoid carcinoma of the hand. *J. Kansas M. Soc.* 49: 100-102, Mar., 1948.—Report of 27 cases.

Conway, Herbert [N. Y. Hosp., & Cornell Univ. M. Coll., New York City]: Evolution of treatment of capillary hemangiomas of the face with further observation on the value of camouflage by permanent pigment injection (tattooing). *Surgery* 23: 389-396, Mar., 1948.—Discussion of techniques and report of 4 cases.

- Gárciga, Carlos E. [Inst. Radium, Havana, Cuba]: Epiteliomas de los párpados. (Su tratamiento roentgenterápico). [Epithelioma of the eyelids (x-ray therapy).] Arch. cubanos cancerol. 6: 245-261, July/Sept., 1947.—Ten case reports.
- Helanen, Sirkka [Univ. Turku, & Prov. Hosp. Hämnenlinna, Fin.]: Peculiar connective tissue tumour of the hairy scalp. (Tactile corpuscle neurinoma). Acta path. et microbiol. Scandinav. 24 (3/4): 299-314, 1947.—Case report.
- Holz, Hans [Univ. Halle, Ger.]: Die Entstehung von Carcinomen bei Acrodermatitis atrophicans. [Development of carcinoma in acrodermatitis atrophicans.] Ztschr. f. Haut- u. Geschlechtskr. 3: 206-213, Sept. 1, 1947.—Case report.
- King, Reginald A.: Malignant melanoma of eyelid with secondary deposits in regional lymphatic nodes. Proc. Roy. Soc. Med. 41: 103-104, Feb., 1948.—Case report.
- Lever, Walter F. [Mass. Gen. Hosp., Boston]: Sebaceous adenoma. Review of the literature and report of a case. Arch. Dermat. & Syph. 57: 102-111, Jan., 1948.
- Linell, Folke [Path. Inst., Univ. Lund, Sweden]: On the tumour-promoting effect of a single mechanical trauma. An experimental study on skin tumours in tarred rabbits. Acta path. et microbiol. Scandinav. Suppl. 71: 1-110 [plus 3 tables], 1947.—In studying the importance of trauma in the development of tar tumors on the skin of rabbits, two types of trauma were used: deep, by punching holes through the rabbit ear (the method used by Rous *et al.*); superficial, by rubbing off only the surface epithelium. The tumor-promoting effect of trauma was studied by comparing the frequency of tumors on traumatized skin with that found on merely tarred skin. Control studies on the method were done. The main findings in the effect of a single trauma were: On rabbit ears, which had been brushed with tar for a month previously, a deep, single mechanical trauma had a distinct tumor-promoting effect, statistically significant during a subsequent tarring period. Superficial, purely epithelial traumas had no demonstrable effect. The effect of a deep trauma was positively correlated to the frequency of tumors on merely tarred skin. Reasons that make it probable that the effect is demonstrable only within a limited space of time are given. A deep trauma on normal skin had no demonstrable tumor-promoting or -inhibiting effect, even if the tarring was commenced immediately after the healing. In view of these results, the time of traumatization in relation to the time of treatment with carcinogens, and the depth of the trauma, most of the previous experimental, apparently contradictory, results may be explained. Studies of the literature likewise seem to show that thermic traumas have, to a great extent, the same effect on the development of tumors as do mechanical traumas, although a more specific carcinogenic effect of thermic traumas cannot be excluded either.—*From Auth. Summ.*
- Macdonald, Ian [Sch. Med., Univ. South. Calif., Los Angeles]: California Cancer Commission Studies. Chapter XI. Cancer of the lip. California Med. 68: 37-42, Jan., 1948.
- Michelson, Henry E. [Univ. Minn., Minneapolis]: Cutaneous cancer. J.A.M.A. 136: 683-686, Mar. 6, 1948.—Prognostic factors, morphological and basic types, development, precancerous lesions, diagnosis, and therapy.—*D. A. S.*
- Miescher, G. [Univ. Zurich, Switz.]: Neuere Erfahrungen auf dem Gebiet der Strahlentherapie der Hautcarcinome. [Recent experiences with x-ray therapy in carcinoma of the skin.] Radiol. clin. 16: 343-378, Nov., 1947.
- Piérard, J. [Brussels, Belg.], & Dupont, A. [Namur, Belg.]: Nodular epithelioma. Brit. J. Dermat. 60: 50-56, Feb., 1948.—Report and discussion of 29 cases.
- Robertson, J. W., & Clement, K. W. [Cleveland City Hosp., Ohio]: Squamous cell carcinoma following prolonged use of arsenic. Case report. Ohio State M. J. 44: 280-281, Mar., 1948.—Carcinoma of finger followed prolonged use of potassium arsenite.
- Ryan, Allan J. [Meriden, Conn.]: Dermoid cyst of the bridge of the nose. Connecticut State M. J. 12: 218-221, Mar., 1948.—Occurrence in 2-yr.-old boy; case report.
- Saint, C. F. M. [Univ. Cape Town, S. Africa]: A clinical atlas. IV. Skin cancer. 3. Melanotic carcinoma. Clin. Proc. 6: 382-390, Nov.; 419-426, Dec., 1947.
- Sims, Charles F., & Kirsch, Neville [N. Y. Post-Grad. M. Sch. & Hosp., New York City]: Spindle cell epidermoid epithelioma simulating sarcoma in chronic radiodermatitis. Arch. Dermat. & Syph. 57: 63-68, Jan., 1948.—Report of 2 cases.
- Way, Stuart C. [San Francisco, Calif.]: Hamartoma of the skin. (A case report.) J. Invest. Dermat. 10: 189-196, Mar., 1948.

NERVOUS SYSTEM

- Alexander, W. S. [Otago M. Sch., New Zealand]: Multiple primary intracranial tumours. Meningioma associated with a glioma; report of a case. J. Neuropath. & Exper. Neurol. 7: 81-88, Jan., 1948.
- Bickford, Reginald G., & Baldes, Edward J. [Rochester, Minn.]: The electroencephalogram in tumors of the posterior fossa. J. Lab. & Clin. Med. 32: 1549-1550, Dec., 1947.
- Bradford, F. Keith [Houston, Tex.]: Heman-gioblastoma of the posterior fossa (Lindau's disease). Report of two cases with familial history. J. Neurosurg. 5: 196-201, Mar., 1948.
- Campbell, Eldridge, & Whitfield, Robert D. [Albany M. Coll., N. Y.]: Posterior fossa meningiomas. J. Neurosurg. 5: 131-153, Mar.,

1948.—Nine cases of meningioma of the posterior fossa arc reported (tumors within the foramen magnum not included). These fell into three main groups according to origin: those of the tentorium, posterior wall and lateral recesses, 5 cases; of the cerebellopontine angle, 1; and of the clivus, 3. The clinical signs are presented. 5 patients are living, 4 dead. The 5 tumors that arose from the under surface of the tentorium, the lateral recess, and the convexity produced symptoms and signs much like tumors of cerebellar origin. Neither upon clinical nor ventriculographic evidence would it have been possible to differentiate them (with 2 possible exceptions). The meningioma of the cerebellopontine angle, like acoustic neuromas, grew slowly and eventually involved the acoustic, facial, and trigeminal nerves; on the contrary, vestibular function of the involved 8th nerve was lost late, and bone erosion was demonstrable in the petrous tip and/or the adjacent clivus. The 3 meningiomas of the clivus involved adjacent nerves early. Compression of the suprajacent pons and medulla was evident, although it was remarkable how large 2 of these tumors had grown without producing greater embarrassment. All eroded bone deeply. One tumor was removed completely and a second subtotally; both patients are living and able to work 9 and 4 years later. The third had a huge angioblastic meningioma which extended forward to encompass the left internal carotid artery; she succumbed 2 days after operation.

(Footnote: Since completion of this study 1 additional case of a meningioma in the right lateral recess penetrating the tentorium and eroding the mastoid has been seen.)—*Auth. Summ. & Concl.*

Craig, Winchell McK. [Mayo Clin., Rochester, Minn.]: Tumors of the spinal cord. *Am. J. Surg.* 75: 69-81, Jan., 1948.

Drew, John H., & Grant, Francis C. [Hosp., Univ. Pa., Philadelphia]: Benign cysts of the brain. An analysis with comparison of results of operative and non-operative treatment in thirty cases. *J. Neurosurg.* 5: 107-123, Mar., 1948.

Ecker, Arthur [Syracuse Univ. Coll. Med., N. Y.]: Upward transtentorial herniation of the brain stem and cerebellum due to tumor of the posterior fossa. With special note on tumors of the acoustic nerve. *J. Neurosurg.* 5: 51-61, Jan., 1948.

Ferey, Daniel [Saint-Malo, France]: A propos des neurinomes en sablier intra-rachidiens et intra-thoraciques et de leur ablation chirurgicale en un temps. [Intraspinal and intrathoracic hour-glass neuromas and their surgical removal in one stage.] *Presse méd.* 55: 659-660, Oct. 1, 1947.

Freedman, Howard, & Forster, Francis M. [Jefferson M. Coll., Philadelphia, Pa.]: Bone formation and destruction in hyperostoses associated with meningiomas. *J. Neuropath. &*

Exper. Neurol. 7: 69-80, Jan., 1948.—The bone growth and destruction seen in hyperostoses of the skull associated with meningiomas is a function of the tumor cells. Such cells can produce fibroblasts, osteoblasts, and osteoclasts or act as the latter two without apparent morphological alteration. The local invasiveness of meningiomas is demonstrated by their growth into the diploe and Haversian canals of the adjacent skull in some cases.—*Auth. Concl.*

French, Lyle A. [Univ. Minn. Hosps., Minneapolis]: Psychometric testing of patients who had brain tumors removed during childhood. *J. Neurosurg.* 5: 173-177, Mar., 1948.—Psychometric tests to determine evidence of mental deterioration were given to 10 patients who previously had been operated upon for removal of a cerebellar tumor. None showed such evidence.—*Auth. Summ.*

Gatewood, John W.; McGuire, L. D.; Johnson, Arthur C., & McCarthy, Harry H. [Creighton Univ. Sch. Med., Omaha, Nebr.]: Unusual complication encountered in removal of large retroperitoneal ganglioneuroma. *Nebraska State M. J.* 33: 170-172, May, 1948—Fifty days after double ligation of the inferior vena cava, the patient died of hemorrhage following a fall—presumably because of a fracture of a clot in the ligated section.—*D. A. S.*

Gotten, Nicholas, & Hawkes, C. D. [Univ. Tenn. M. Sch., Memphis]: Important factors in the diagnosis of favorable brain tumors. *J. Tennessee State M. A.* 41: 80-86, Mar., 1948.

Kaplan, Abraham [Hosp. Joint Dis., New York City]: Neurofibroma of cauda equina causing recurrent "sciatica" for twenty years. *Bull. Hosp. Joint Dis.* 8: 155-159, Oct., 1947.—Case report.

Krüger, D. W. [Bundesstaatl. Krankenanst. Bad Ischl.]: Gibt es Möglichkeiten, die frühzeitige Erkennung eines raumneinengenden Prozesses des Schädellinnern zu fördern? (Unter besonderer Berücksichtigung der Konvexitätsmeningeome.) [Are there means to further the early recognition of space-reducing processes in the interior of the skull? (With special reference to meningiomas of the convexity.)] *Krebsarzt* 3: 41-54, Feb., 1948.—Meningiomas comprise about 16% of all brain tumors; $\frac{2}{3}$ develop in the convexity, sinus, or the falx; and most often between the 30th and 50th yrs. Early diagnosis and radical operation lead to cure. Early diagnosis is difficult since the prodromal stage has few symptoms. A long history is usually dominated by headaches; such patients should have x-rays since these reveal bone changes in 50%; the prognosis is doubtful. A short history usually shows symptoms of irritation or paralysis; the prognosis is good. 8 case reports are given.—*M. C. J.*

Lindgren, Erik [Serafimer Hosp., Stockholm, Sweden]: The normal temporal horn and its deformities by tumours in the middle cere-

- bral fossa. (Abstract) *Proc. Roy. Soc. Med.* 40: 859-862, Dec., 1947.—The complete report will appear as a supplement to *Acta Radiologica*, 1948.
- Loeliger, H. Th. [Univ. Zurich, Switz.]: *Ueber Fazialisneurinome. (Anhand von zwei eigenen Fällen.)* [Facial neurinoma. (Two unusual cases.)] *Acta oto-laryng.* 35 (5/6): 543-555, 1947.
- Lundgren, Nils [Ear, Nose & Throat Clin., Lund, Sweden]: *Neurinoma n. facialis.* *Acta oto-laryng.* 35 (5/6): 535-537, 1947.—Case report.
- McGovern, V. J. [Univ. Sydney, & Roy. Prince Alfred Hosp., Sydney, Australia], & Wyke, B. D.: *Haemangioxiomoma of the brain: a study of eight cases of so-called "pseudo-xanthomatous" haemangioblastoma.* *M. J. Australia* 1: 297-302, Mar. 6, 1948.—Eight cases of hemangioxiomoma are described. In 1, the tumor was in the medulla oblongata. The remaining tumors were located in the cerebellum; 1 presented clinical and histological evidence of malignancy. The relevant literature is briefly reviewed. It is suggested that the xanthomatous cells are the type cells of this variety of tumor, for which reason the name "hemangioxiomoma" is proposed, and that such tumors represent a cerebral form of reticulo-endotheliosis.—*Auth. Summ.*
- Mallows, H. R. [Roy. Navy, Eng.]: *A case of cerebellar tumour simulating pyloric obstruction.* *Brit. M. J.* 2: 999, Dec. 20, 1947.—*Spongiblastoma.*
- Meredith, J. M. [M. Coll. Va., Richmond]: *The elimination of non-surgical lesions in brain tumor suspects. (A) Pseudo-tumor cerebri, and (B) papilledema without increased intracranial pressure (optic neuritis).* *South. M. J.* 41: 31-37, Jan., 1948.
- Naffziger, Howard C., & Boldrey, Edwin B. [Univ. Calif. M. Sch., San Francisco]: *Cancer of the nervous system. Brain, spinal cord and peripheral nerves.* *J.A.M.A.* 136: 96-108, Jan. 10, 1948.—A discussion of growth characteristics, diagnosis, and treatment of tumors of the brain, spinal cord, and peripheral nerves, with emphasis on gliomas, meningiomas, cerebellopontine-angle tumors, and pituitary tumors.—*D. A. S.*
- Parkinson, Dwight [Dartmouth M. Sch., Hanover, N. H.]: *Fibrillary (pilocytic) astrocytoma in the floor of the fourth ventricle.* *Arch. Neurol. & Psychiat.* 58: 606-609, Nov., 1947.—Case report.
- Picaza, Jorge A., & Baker, George S. [Mayo Clin., Rochester, Minn.]: *Multiple meningiomas: report of case and surgical considerations.* *Proc. Staff Meet., Mayo Clin.* 23: 54-56, Jan. 21, 1948.
- Shenkin, Henry A.; Grant, Francis C., & Drew, John H. [Hosp., Univ. Pa., Philadelphia]: *Postoperative period of survival of patients with oligodendroglioma of the brain. Report of twenty-five cases.* *Arch. Neurol. & Psychiat.* 58: 710-715, Dec., 1947.—Six of the present series of 25 oligodendrogliomas (24%) were located principally within a lateral and/or the third ventricle. 17 of the 19 oligodendrogliomas growing in the parenchyma of the brain were located in one or the other, or in both frontal lobes. Patients with ventricular tumors had a short preoperative course (av. $7\frac{1}{2}$ mos.), and the symptoms were those of increased intracranial pressure. Patients with hemispheric tumors had a longer preoperative duration of symptoms (av., 35 mos.), and the history generally was one of focal symptoms, often jacksonian seizures, preceding the symptoms and signs of increased intracranial pressure. The average period of survival after operation in this series was less than 2 yrs. Of the 5 patients with ventricular tumor who survived operation, only 1 is still alive and well (at the end of 50 mos.). The average period of survival of the remaining 4 patients was $12\frac{1}{2}$ mos., with a range of 2 to 23 mos. 15 patients with hemispheric tumor recovered from operation, but only 4 are still alive, 10 to 30 mos. later. The remaining members of this group survived an average of 22 mos., with a range varying from 5 to 48 mos.—*Auth. Summ.*
- Ward, Arthur, & Spurling, R. Glen [Univ. Louisville Sch. Med., Ky.]: *The conservative treatment of third ventricle tumors.* *J. Neurosurg.* 5: 124-130, Mar., 1948.—In all patients in whom the symptoms, neurological signs, and ventriculogram conclusively demonstrate the presence of a third ventricle tumor (other than a colloid cyst), a subtemporal decompression is performed and this is followed by intensive irradiation. In those cases in which the patient fails to respond to this conservative regimen, a direct surgical attack on the lesion is carried out. In this way, the occasional cyst (colloid or of the septum) will be demonstrated, and subtotal removal of malignant lesions with histological verification can be carried out. 14 patients have been so treated. Of these, 2 failed to respond; subsequent reoperation disclosed cysts, which were removed. 6 patients had malignant gliomas which were proved at subsequent reoperation and 5 died within 3 yrs. Finally, 6 patients (including 3 with probable pineal tumors) treated in this manner did well and all are at present living.—*Auth. Summ.*
- Welch, C. Stuart; Ettinger, Alice, & Hecht, Paul L. [Tufts Coll. M. Sch.; Boston Dispensary, & Joseph H. Pratt Diagnostic Hosp., Boston, Mass.]: *Recklinghausen's neurofibromatosis associated with intrathoracic meningocele. Report of a case.* *New England J. Med.* 238: 622-625, Apr. 29, 1948.

EYE AND EAR

Calhoun, F. Phinazy, Jr. [Atlanta, Ga.]: *Pigmented lesions of the eye and adnexae.* *J. M. A. Georgia* 37: 140-142, Apr., 1948.

- Dubs, Paul [Hôp. St.-Antoine, Paris, France]: Primary carcinoma of the external auditory meatus. *Brit. M. J.* 1: 50, Jan. 10, 1948.—Three case reports.
- Iliff, Charles E. [Johns Hopkins Hosp. & Univ., Baltimore, Md.]: Beta ray radium applicator for ocular use: preliminary report. *Arch. Ophth.* 38: 827-830, Dec., 1947.
- Kennedy, Robert E. [Johns Hopkins Hosp. & Univ., Baltimore, Md.]: Cystic malignant melanomas of the uveal tract. *Am. J. Ophth.* 31: 159-167, Feb., 1948.
- Loewenstein, Arnold, & Foster, John [Tennent Inst., Glasgow, Scotland]: Two unusual sclero-corneal neoplasms. *Brit. J. Ophth.* 32: 1-12, Jan., 1948.—A spindle-cell sarcoma and a benign fibroma; possible virus etiology is discussed.—*M. C. J.*
- Miller, Douglas, & Dowling, J. L. [Sydney, Australia]: Orbital hydatid. *Brit. J. Surg.* 35: 211-212, Oct., 1947.—Case report.
- Moulton, E. C., & Moulton, E. C., Jr. [Fort Smith, Ark.]: Leiomyoma of the iris. *Am. J. Ophth.* 31: 214-217, Feb., 1948.
- Philps, A. S.: Melanosis of conjunctiva. *Proc. Roy. Soc. Med.* 41: 66, Jan., 1948.—Case report.
- Schulz, Milford D., & Heath, Parker [Mass. Gen. Hosp., Boston]: Lymphoma of the conjunctiva. *Radiology* 50: 500-505, Apr., 1948.—An analysis of 14 cases of conjunctival lymphoma (0.9% of 1500 tumors of the ocular adnexa) is presented. Cytologically they are most often lymphocytoma. The histological character seems to have no conclusive bearing upon the prognosis. These tumors occur more often in older age groups; they respond well to x-rays in minimal doses; if the tumor is localized, x-ray treatment or surgical removal is followed by a long period of remission. The clinical course of the 14 patients is charted.—*D. A. S.*
- Urbantschitsch, Ernst [Krankenanst. Rudolfstift., Vienna, Austria]: Über Ohrenkrebs mit besonderer Berücksichtigung der Entwicklung und des Verlaufes der Basalzellen-Karzinome im Bereiche des Gehörorganes. [Cancer of the ear with special reference to development and course of basal-cell carcinoma in the auditory area.] *Monatschr. f. Ohrenh.* 81: 526-544, Sept./Oct./Nov., 1947.—Three case reports; carcinoma spread from external ear toward or into middle ear.—*M. C. J.*
- Whittington, T. H.: Leucosarcoma of iris (unpigmented malignant melanoma). *Proc. Roy. Soc. Med.* 41: 65-66, Jan., 1948.—Case report.
- Blumenthal, H., & Brunner, H. [Univ. Ill., Coll. Med., Chicago]: Intraosseous tumors of the maxilla. *Am. J. Orthodontics* 33: 815-827, Dec., 1947.—Report of 2 cases.
- Brailsford, James F. [Roy. Cripples & Queen Elizabeth Hosps., Birmingham, Eng.]: The serious limitations and erroneous indications of biopsy in the diagnosis of tumours of bone. *Proc. Roy. Soc. Med.* 41: 225-236, Apr., 1948.
- Bustos, Fernando M., & Brachetto-Brian, Domingo; Cordoma de 5ª vértebra lumbar. [Chordoma of the 5th lumbar vertebra.] *Bol. y trab., Acad. argent. de cir.* 31 (21): 738-744, 1947.—Case report.
- Coley, Bradley L., & Higinbotham, Norman L. [New York City]: Conservative surgery in tumors of bone with special reference to segmental resection. *Ann. Surg.* 127: 231-242, Feb., 1948.
- Copello, Oscar: Condroosteoblastoma del hueso ilíaco con degeneración maligna. [Chondroblastoma of the ilium with malignant degeneration.] *Bol. y trab., Acad. argent. de cir.* 31 (26): 899-901, 1947.—Case report.
- Flink, Edmund B. [Univ. Minn., Minneapolis]: Calcium, phosphorus and phosphatase as aids in the diagnosis of bone lesions. *Radiology* 50: 72-82, Jan., 1948.
- Garland, L. Henry, & Kennedy, Bayles R. [Stanford Univ. M. Sch., San Francisco, Calif.]: Roentgen treatment of multiple myeloma. *Radiology* 50: 297-317, Mar., 1948.—Survey of literature and report of 13 cases.
- Gentil, Fernando, & Coley, Bradley L. [Memorial Hosp., New York City]: Sacrococcygeal chordoma. *Ann. Surg.* 127: 432-455, Mar., 1948.—Seven cases of sacrococcygeal chordoma seen between 1930 and 1943 are analyzed; 128 cases, reported by others, reviewed. This tumor is rare: during the same period more than 30,000 patients with neoplastic disease were admitted to Memorial Hospital. It arises from notochordal tissue, grows slowly and progressively; tends to destroy bone, recurs promptly following surgical excision, and, in general, is radioresistant. Histologically, it is well differentiated and of relatively low malignancy; highly malignant types occur occasionally, accounting for widespread metastasis in about 10% of the cases (lungs, liver, peripheral lymph nodes). Pain is the earliest symptom, becomes intractable when nerve roots are involved, and is present in half the cases before a mass is noted. Bladder and rectal disturbances, trophic ulcers, and other neurological manifestations appear during the more advanced stages. Destruction of the sacrum is a constant feature. Chordoma must be differentiated from chondrosarcoma and tuberculosis of the sacrum; tumors of the female pelvic organs, spinal cord, and soft parts; sacrococcygeal teratoma; cancer of the rectum. Although x-rays are helpful for clinical differentiation, a definite diagnosis can be made only by biopsy. Because of the anatomical location

OSSEOUS SYSTEM

- of the tumor, surgical resection is difficult. Removal of bulky portions, radiation therapy to control pain, and chordotomy are recommended. A cure has never been obtained; palliation is the most that can be hoped for with present methods of therapy.—*H. E. E.*
- Goldenberg, Raphael R. [St. Joseph Hosp., Paterson, N. J.]: Osteoid-osteoma. *J. M. Soc. New Jersey* 45: 104-107, Mar., 1948.—Report of 4 cases.
- Gutman, Alexander B. [Columbia Univ. Coll. Phys. & Surgeons, New York City]: Tumors of the skeletal system: medical aspects. *Bull. New York Acad. Med.* 23: 512-518, Sept., 1947.
- Kibler, Raymond S. [Univ. Buffalo Sch. Med., N. Y.]: Myeloma cell cytology as revealed by histochemical methods. *J. Lab. & Clin. Med.* 32: 1428-1429, Nov., 1947.—The areas of hyaloplasm in the myeloma cells are due to the presence of underlying mitochondria and portions of the Golgi element. These structures have been found to be of a phospholipid nature. Vitamin A and/or the carotinoid pigments are localized to these areas. These structures give a cytochemical reaction for free alpha amino-acid groups.—*Auth. Summ.*
- Kinkade, Joseph M. [Tucson, Ariz.]: Angiosarcoma of the petrous portion of the temporal bone. Report of a case. *Ann. Otol., Rhin. & Laryng.* 57: 235-240, Mar., 1948.
- Kinsella, Thomas J.; White, S. Marx, & Koucky, R. W. [Minneapolis, Minn.]: Two unusual tumors of the sternum. *J. Thoracic Surg.* 16: 640-667, Dec., 1947.—Two unusual sternal tumors, a benign giant-cell and an apparently solitary plasma-cell myeloma, are presented, and surgical treatment outlined. The available literature on benign, malignant, and metastatic tumors and some of the inflammatory lesions of the sternum is reviewed and tabulated.—*Auth. Summ.*
- Lapidus, Paul W., & Wilson, Milton J. [Flower & Fifth Ave. Hosps., New York City]: Osteoid osteoma. Report of three cases. *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* 10: 37-44, 1947.
- Lattes, Raffaele, & Bull, David C. [Columbia Univ. & Presbyterian Hosp., New York City]: A case of glomus tumor with primary involvement of bone. *Ann. Surg.* 127: 187-191, Jan., 1948.
- Manganicillo, Louis O. J.; Reimann, D. L., & Wagner, John A. [Univ. Md. Sch. Med., Baltimore]: Cerebral involvement by osteogenic sarcoma associated with Paget's disease of the skull. *Arch. Neurol. & Psychiat.* 59: 99-106, Jan., 1948.—Case report.
- Morton, John J., & Mider, G. Burroughs [Univ. Rochester, Sch. Med. & Dent., N. Y.]: Chondrosarcoma. *Ann. Surg.* 126: 895-931, Dec., 1947.—Discussion and report of 14 cases.
- Phemister, Dallas B. [Univ. Chicago, Ill.]: Cancer of the bone and joint. *J.A.M.A.* 136: 545-554, Feb. 21, 1948.—Diagnosis and treatment of osteogenic sarcoma, chondrosarcoma, fibrosarcoma, malignant giant-cell tumor, Ewing's sarcoma, reticulum-cell sarcoma, lymphosarcoma, angiosarcoma, liposarcoma, myeloma, and synovoma.—*D. A. S.*
- Poppe, J. K., & Berg, R. [Portland Veterans Adm. Hosp., Portland, Oreg.]: Resection of chest wall tumors. Report of two cases. *Northwest Med.* 47: 119-122, Feb., 1948.
- Seeman, George F. [Nashville, Tenn.]: Sacrococcygeal cystic teratoma with traumatic hemorrhage. *Oral Surg., Oral Med. & Oral Path.* 1: 308-311, Mar., 1948.
- Shellito, John G., & Dockerty, Malcolm B. [Mayo Clin., Rochester, Minn.]: Cartilaginous tumors of the hand. *Surg., Gynec. & Obst.* 86: 465-472, Apr., 1948.—Analysis of 42 cases.
- Sherman, Robert S., & Snyder, Ruth Evelyn [Memorial Hosp., New York City]: The roentgen appearance of primary reticulum cell sarcoma of bone. *Am. J. Roentgenol. & Rad. Therapy* 58: 291-306, Sept., 1947.—From findings on 17 cases, the authors conclude that primary reticulum-cell sarcoma of bone is a radio-sensitive tumor presenting constant features of single-bone involvement, medullary origin, medullary and cortical bone destruction, moderately active growth, ill-defined borders, characteristic changes in x-rays following x-ray therapy, a tendency to grow within the medullary portion of the bone with relatively small periosteous extension, and a predilection for the long bones, more than 40% of all cases being located about the knee. Osteogenic sarcoma bears the closest resemblance to reticulum-cell sarcoma, especially when of medullary origin. When it occurs in the shaft, Ewing's tumor may have to be considered in differential diagnosis. In 15 of these 17 cases, x-rays were the sole method of treatment. It was used once with local excision; once it preceded amputation.—*A. G. James, M.D.*
- Srivastava, S. P. [M. Coll., Agra, India]: Hydatid cyst of innominate bone. *Indian J. Surg.* 9: 157-158, Sept., 1947.—Case report.
- Tamari, M. [Chicago, Ill.]: Mastoid bone biopsies. *Ann. Otol., Rhin. & Laryng.* 56: 999-1006, Dec., 1947.
- Valls, Jose; Ottolenghi, Carlos E., & Schajowicz, Fritz [Buenos Aires, Argentina]: Aspiration biopsy in diagnosis of lesions of vertebral bodies. *J.A.M.A.* 136: 376-382, Feb. 7, 1948.—The technique, indications, and end results obtained by aspiration biopsy of the vertebral bodies are given. Not all the vertebral segments are recommended for puncture, and in certain regions, such as the upper dorsal, large arterial and venous trunks could be injured. Two areas best suited for aspiration are: an upper group comprising the 4 distal cervical vertebrae; a lower group, the 3 distal dorsal and

all the lumbar vertebrae. The technique of aspiration and special needles required are described. There were no significant accidents, probably because of the technique employed. This was used in 86 cases in these regions: cervical in 9, dorsal in 18, lumbar in 46, and undesignated in 13 cases. The types of lesions in 68 of these cases were: metastatic cancer 32, myeloma 9, angioma 1, tuberculosis 12, echinococcus 2, inflammatory and other non-specific diagnoses 12. Definitely positive diagnoses were made in 59 cases by smear and section of the aspirated material.—*F. S. Butler, M.D.*

RESPIRATORY TRACT

NOSE : SINUSES : PHARYNX

Adams, W. Stirk [Birmingham, Eng.]: A case of chordoma of the right frontal sinus. *J. Laryng. & Otol.* 62: 93-95, Feb., 1948.

Cojazzi, Luigi [Univ. Padua, Italy]: Ricerche sulle reazioni reticolari iperplastiche e neoplastiche nelle vie aeree superiori. Nota III. Le reazioni del reticolo endotelio nelle linfoghiandole latero-cervicali durante lo sviluppo di neoplasmi oro-faringo-laringei. [Hyperplastic and neoplastic reticular reaction in the upper respiratory passages. III. The reaction of the reticulo-endothelium in the lateral cervical lymph glands during the development of oro-pharyngo-laryngeal neoplasms.] *Arch. ital. di otol.* 58: 166-172, Sept., 1947.

Cornthards, A. E. [Phoenix, Ariz.]: Angio-epithelioma of the postnasal space. *Ann. Otol., Rhin. & Laryng.* 57: 230-234, Mar., 1948.—Case report.

Graham, Vincent P., & Meyer, Ralph R. [Univ. Chicago, Ill.]: Experiences with nasopharyngeal carcinoma. *Radiology* 50: 83-91, Jan., 1948.—Twenty-six proved cases of malignant neoplasms of the nasopharynx are reviewed. Transitional-cell carcinoma was the commonest lesion. Cervical lymphadenopathy was present in the majority of the patients on the initial examination. 18 of the 24 patients examined by axial x-rays of the skull showed bone destruction, most frequently in the region of the petrous apex and foramen ovale. External x-rays were used in all cases as the only treatment, 5000 r in 40 days being the usual tumor dose. 17 patients are now dead, the average survival period from the time of treatment being 23 mos. Of those still living, 4 are free of disease 5 yrs. or longer, 1 is well after 3 yrs., 1 was apparently well for 12 yrs., and now has a local recurrence; the remaining 3 patients were alive when last seen but are not expected to survive.—*Auth. Summ.*

McFarland, J. C. [Roy. Liverpool Children's Hosp., Eng.]: Retropharyngeal lipoma. Report of a case. *Lancet* 1: 327, Feb. 28, 1948.

McKenzie, W. Raymond [Baltimore, Md.]: Ma-

lignancy of the nasal sinuses. *South. M. J.* 41: 156-158, Feb., 1948.—A review.

Martin, Hayes; Ehrlich, Harry E., & Abels, Jules C. [Memorial Hosp., New York City]: Juvenile nasopharyngeal angiofibroma. *Ann. Surg.* 127: 513-536, Mar., 1948.—This rare, highly vascular, essentially benign neoplasm, encountered in 29 patients from 1927 to 1946, occurs in pubescent males and usually regresses spontaneously when full sexual maturity has been reached. Evidence is presented to support a sex-endocrine relationship. There were no instances of malignant transformation; the authors believe that those cases previously reported by others as malignant were not critically selected. The usual symptoms are nasal obstruction, recurrent epistaxis, facial deformity, and unilateral exophthalmos. Paranasal sinus and ear infections are frequent complications. The presence, in pubescent or adolescent males, of a bulky, vascular nasopharyngeal mass that has grown forward to block one or both choana and is associated with these symptoms should suggest the diagnosis, and biopsy taken for histologic confirmation.

Treatment comprises relief of symptoms and arrest of the growth, during the period of activity, since complete eradication, either by surgery or irradiation, is impossible and attempts thereat hazardous. A systematic plan of treatment is outlined: hormone therapy (testosterone propionate), ligation of the external carotid arteries, x-ray and radium therapy. Surgical removal of the bulk of the tumor through a transmaxillary approach is described but recommended only in patients with marked facial deformity or with symptoms that cannot be controlled by more conservative methods of treatment. The prognosis is excellent if the case is properly managed. The greatest hazard to life and permanent disability lies in injudicious treatment.—*H. E. E.*

Révész, G. [St. Rochus Hosp., Budapest, Hung.]: Neurinoma in the nasal cavity. *J. Laryng. & Otol.* 62: 241-244, Apr., 1948.—Case report.

Shea, John J. [Memphis, Tenn.]: The pathology of nasal polyps and related growths. *Ann. Otol., Rhin. & Laryng.* 56: 1029-1034, Dec., 1947.

Suggitt, Stephen: Three cases with extensive carcinoma of the hypopharynx. *J. Laryng. & Otol.* 62: 245-248, Apr., 1948.

Van Metre, Thomas E., Jr. [Johns Hopkins Hosp. & Sch. Med., Baltimore, Md.]: Malignant tumors of the nasopharynx. *Bull. Johns Hopkins Hosp.* 82: 42-55, Jan., 1948.—The author has analyzed 46 cases of malignant nasopharyngeal tumors collected over a period of 21 yrs., to emphasize and explain certain signs and symptoms associated with these lesions. As demonstrated in this study, the delay in diagnosis is not warranted on the basis of the evident clinical picture. In 94%, the first symptom fell in one of four groups. In the "ear group" as manifested by pain, tinnitus, fullness, air-conduction

- deafness, or retraction of the drum, there was an average delay of 20½ mos. from the appearance of the first symptom to admission. In those with "nose symptoms" such as pain, obstruction to breathing, or nasal, often bloody, discharge, there was an average delay of 14 mos. Even in the "node group" where a subdiaphragmatic node, often bilateral, was the patient's first complaint, an average of 13 mos. (up to 2 yrs.) elapsed before admission for diagnosis. In the group of "cranial nerve involvement" there was an average delay of 7 mos. This shorter period was accounted for by the fact that in almost every case in this category, pain was a first and continuously prominent symptom. All except the XI cranial nerve were involved singly or in combination in this series. Most frequently affected were the V (27 times), VI (13), IX (13), VII (10) and XII (8). Surprisingly, the III and IV cranial nerves were involved only 6 and 3 times, respectively. In the nasopharynx, the tumor most often spread through the foramen lacerum and laterally along the sella turcica and cavernous sinus where the III, IV, V, and VI cranial nerves are readily encountered. Further extradural and intracranial spread would account for the involvement of the other cranial nerves. In fact, the detailed tables reveal that wherever cranial nerves other than III, IV, V, and VI were involved, one or more of the latter were also affected. [A thorough study and awareness of the many points emphasized by this paper should materially tend to cut down the unnecessarily long delay now encountered between the appearance of the first symptom and the final diagnosis in malignant tumors of the nasopharynx.]—*S. L. Perzik, M.D.*
- Waltner, Jules G. [Columbia Univ., Coll. Phys. & Surgeons, New York City]: Plasma cell tumors of the nasopharynx. *Ann. Otol., Rhin. & Laryng.* 56: 911-916, Dec., 1947.—Report of 2 cases of plasmocytoma.
- ### LARYNX
- Charteris, Alexander A. [Glasgow, Scotland]: Cancer of the larynx and its treatment by radium. *J. Laryng. & Otol.* 62: 163-169, Mar., 1948.—Analysis of 30 cases.
- Clerf, Louis H. [Jefferson Hosp., Philadelphia, Pa.]: Laryngectomy. *Surg., Gynec. & Obst.* 86: 197-202, Feb., 1948.—Discussion of indications, technique, and results.
- Donlan, Charlotte P. [New York City]: Tumor dose in cancer of the larynx. *Radiology* 50: 463-467, Apr., 1948.—A study of 113 cases.
- Etter, H. [Röntgen-Inst., Kantonsspital, Lucerne, Switz.]: Die perorale Nahbestrahlung der Larynx- und Hypopharynx-Carcinome. [Peroral short-distance irradiation in laryngeal and hypopharyngeal carcinoma.]: *Radiol. clin.* 16: 337-338, Nov., 1947.
- Harris, Herbert H. [Houston, Tex.]: Benign lesions of the true vocal cords. *Ann. Otol., Rhin. & Laryng.* 57: 189-196, Mar., 1948.—General discussion.
- Jesberg, Simon [Los Angeles, Calif.]: California Cancer Commission Studies. Chapter XIV. Cancer of the larynx. *California Med.* 68: 303-305, Apr., 1948.
- Kemler, Joseph I. [Baltimore, Md.]: Treatment of carcinoma of the pharynx and larynx. *Eye, Ear, Nose & Throat Monthly* 27: 119-125, Mar., 1948.—Analysis of 50 cases.
- Kernan, John D. [Coll. Phys. & Surgeons, Columbia Univ., New York City]: The treatment of intrinsic cancer of the larynx. *New York State J. Med.* 48: 178-182, Jan. 15, 1948.
- Proctor, Bruce; Lofstrom, James E., & Nurnberger, Carl E. [St. Mary's Hosp., & Wayne Univ. Coll. Med., Detroit, Mich.]: The use of contact therapy in the treatment of carcinoma of the larynx. *Laryngoscope* 58: 225-243, Mar., 1948.—This is a preliminary report of a new, combined surgical and radiation treatment of cancer of the larynx. Contact x-rays, with the Phillips unit, are given to the tumor bed after tumor removal by a laryngofissure (factors: 50 K.V.P.; 0.2 to 1.2 mm. Al; 2.0 to 4.0 cm. STD; 1.0 to 3.0 cm. fields, giving 5000 to 12,000 r). Of the 9 cases of intrinsic cancer of the larynx, only 2 showed histologic proof of residual cancer in the tumor bed; 1 revealed recurrent disease at 4½ mos. requiring total laryngectomy. External fistulas developed in 4 cases, 2 with limited chondritis; all eventually closed. The resulting voice was husky in all cases. Isodose charts through the neck at the vocal-cord level are presented for high-voltage x-rays, the Phillips contact unit, and the radium pack. The longest follow-up is 21 mos. [The short follow-up and the absence of histologic evidence of cancer in the tumor bed in 7 of the 9 cases, with a prompt recurrence in 1 of the 2 cases showing residual cancer, should be considered before applying this combined treatment to operable cases.]—*S. L. Perzik, M.D.*
- Putney, F. Jolinson [Philadelphia, Pa.]: Hoarseness. *J. M. Soc. New Jersey* 45: 23-26, Jan., 1948.
- Schall, LeRoy A., & Jesberg, Norman [Mass. Eye & Ear Infirmary, Boston]: Unusual laryngeal lesions. *Ann. Otol., Rhin. & Laryng.* 56: 904-910, Dec., 1947.—Report of 3 cases: bronchogenic carcinoma with carcinoma of larynx 9½ yrs. later; carcinoma of larynx recurring in identical location 8 yrs. after simple biopsy: localized primary idiopathic amyloid disease confined to the larynx.—*D. A. S.*
- Schoolman, Joseph G. [Chicago, Ill.]: Mortality in cancer of the larynx. *Ann. Otol., Rhin. & Laryng.* 57: 197-200, Mar., 1948.—Because of patient and physician procrastination, only 15.67% of individuals having cancer of the larynx can be expected to survive 5 or more yrs. The incidence of 44.18% benign laryngitis and the relatively high incidence of surgical cure of operated cases give the patient

and the physician a false sense of security.—
From Auth. Summ.

Tice, Galen M., & White, Charles M. [Univ. Kansas M. Center, Kansas City]: Cancer of the larynx and hypopharynx. *J. Kansas M. Soc.* 49: 93-97, Mar., 1948.

Walker, James S. [Carle Hosp. Clin., Urbana, Ill.]: Neurinoma of the larynx. Report of a case. *Ann. Otol., Rhin. & Laryng.* 56: 898-903, Dec., 1947.

Wiethe, C. [Univ. Vienna, Austria]: Mycosis (Granuloma) fungoides laryngis. *Monatschr. f. Ohrenh.* 81: 501-504, Sept./Oct./Nov., 1947.—Case report.

TRACHEA AND BRONCHI

Broyles, Edwin N. [Baltimore, Md.]: Bronchoscopic experiences with tumors of the lower respiratory tract. *Ann. Otol., Rhin. & Laryng.* 57: 129-133, Mar., 1948.—With presentation of 5 cases illustrating important points in diagnosis.

Clerf, Louis H. [Jefferson Hosp., Philadelphia, Pa.]: Progress in bronchology. *J.A.M.A.* 136: 733-736, Mar. 13, 1948.

Colson, G. M., & Willcox, A. [Middlesex Hosp., Eng.]: Phalangeal metastases in bronchogenic carcinoma. *Lancet* 1: 100-102, Jan. 17, 1948.—Clinical and x-ray evidence of primary bronchogenic carcinoma was present in all 3 patients. In one, metastases to 3 distal hand phalanges were a terminal event; autopsy showed an oat-cell bronchogenic carcinoma. Initially, the others had painful fingers or toes somewhat suggestive of inflammation, but with local enlargement much more prominent than pain. A distal thumb phalanx and a metatarsal were affected in one, a metatarsal in the other. Both showed bone destruction radiographically and malignant cells on aspiration biopsy. In one, these cells had characteristics of lung cancer. Symptoms of the pulmonary disease followed in 6 and 8 wks. Death ensued 24, 7, and 4 mos. from onset of symptoms.—*J. L. Pool, M.D.*

Gagnon, E. D. [Univ. Toronto & Toronto Gen. Hosp., Ont.]: Bronchogenic carcinoma. (12 year review and operative results.) *Canadian M. A. J.* 58: 25-29, Jan., 1948.—A detailed statistical report is presented on 508 cases of bronchogenic carcinoma seen at the Toronto General Hospital, 1934-1945 inclusive. The diagnosis was clinically obvious or proved by biopsy of distant metastasis in 284 patients; in 224, histologic proof came from the primary; in 60, from autopsy. Bronchoscopy was done in 150 and abnormalities noted in 124. A positive biopsy was secured 105 times (69.1%). 88.9% of the patients were male. The age span was 15 to 84 yrs. Thoracotomy was done in 86, with 49 resections. There were 5 lobectomies; only 1 patient had lung cancer and he died of empyema. 2 had adenomas and 2 had lung abscesses, all misdiagnosed preoperatively. The

author definitely excludes 4 cases of malignant adenoma from the pneumonectomy statistics. The 44 pneumonectomies for lung cancer carried an over-all postoperative mortality of 36.3%, or 16 cases. The postoperative complications included embolus to undisclosed sites 6 times, empyema and massive hemorrhage 3 times each. Not a single instance of bronchopleural fistula was noted. Bronchial-stump closure was by a simple running chromic catgut suture reinforced in some cases with interrupted silk sutures. [No pleural overlap is mentioned.] 15 patients survived the operation to die of their cancer, 53% within 6 mos; the longest survival was 2½ yrs. In 5 patients, cerebral metastasis without intrathoracic recurrence was the terminal event. The most significant facts concerning the 13 patients surviving without evident disease are that only 3 had hilar-node metastasis at operation, and 6 had such peripherally situated cancers that bronchoscopy was either negative or not carried out at all. 2 patients died of other causes 4½ and 6 yrs. after pneumonectomy and 3 are still alive more than 5 yrs. after.—*J. L. Pool, M.D.*

Herve, A., & Ramioul H. [Univ. Liège, Belg.]: La radiothérapie dans le cancer bronchique. [Radiotherapy in cancer of the bronchus.] *Rev. méd. Liège* 2: 510-514, Sept. 15, 1947.—A review.

Janes, Robert M. [Toronto, Ont.]: Lipoid pneumonia simulating bronchogenic carcinoma. *J. Thoracic Surg.* 16: 451-457, Oct., 1947.—Report of 2 cases.

Knight, John S., & Bunting, Williston P. [Kansas City, Mo.]: Fibroma of the trachea. *Arch. Otolaryng.* 47: 67-70, Jan., 1948.—Case report.

Langston, Hiram T., & Fox, Robert T. [Northwest. Univ. M. Sch., Chicago, Ill.]: The indication for posterior transpleural bronchotomy in the management of intrabronchial tumors. *Surg., Gynec. & Obst.* 86: 192-196, Feb., 1948.—A case is reported in which a benign pedunculated intrabronchial tumor (fibroma) was managed by transpleural bronchotomy with excellent results. A general discussion of the posterior transpleural surgical approach is presented and a few technical considerations arising from the experience in this case are pointed out.—*Auth. Summ.*

Langston, Hiram T., & Fox, Robert T. [Chicago, Ill.]: Intrabronchial fibroma managed by posterior transpleural bronchotomy. *Proc. Inst. Med. Chicago* 17: 53, Feb. 15, 1948.

Linard, Raymond: Aspects particuliers du cancer bronchique. [Special aspects of bronchial cancer.] *Rev. méd. Liège* 2: 525-528, Sept. 15, 1947.—A review.

Mathews, W. H. [Montreal Gen. Hosp., Que.]: The examination of sputum for tumour cells. *Canadian M. A. J.* 58: 236-240, Mar., 1948.—The method used and the results achieved in the examination of sputum for tumor cells in

- suspected cases of bronchogenic carcinoma in a 2-yr. period are reviewed. A positive diagnosis was made in 24 (72.7%) of 33 cases, either proved or reasonably certain of being a bronchogenic carcinoma. A false positive diagnosis was made once in each of 2 cases. There were 9 in which the sputum was not demonstrated to contain tumor cells, 7 of these being proved by autopsy, biopsy, or operation, and 2 cases having a probable clinical and radiological diagnosis of bronchogenic carcinoma.—*Auth. Summ.*
- Norris, Charles M. [Temple Univ., Philadelphia, Pa.]: Early clinical features of bronchogenic carcinoma: illustrative cases. *Dis. of Chest* 14: 198-217, Mar./Apr., 1948.
- Pavlovsky, Alejandro J.: Adenocarcinoma bronquial. Síndrome de Bamberger-Marie. Neumonectomía. [Bronchial adenocarcinoma. Bamberger-Marie syndrome. Pneumonectomy.] *Bol. y trab., Acad. argent. de cir.* 31 (25): 857-860, 1947.—Case report.
- Scott, Thornton [Lexington, Ky.]: Cytologic studies of sputum in bronchogenic carcinoma. *J. Lab. & Clin. Med.* 32: 1543, Dec., 1947.
- Smathers, Homer M. [Wayne Univ. Coll. Med., Detroit, Mich.]: Cytologic study of bronchial secretions in diagnosis of bronchogenic carcinoma. A short review. *J. Michigan State M. Soc.* 47: 393-395; 452, Apr., 1948.
- Wenzl, M. [II. Chir. Univ.-Klin., Vienna, Austria]: Zur Symptomatologie und Diagnostik des Bronchuskarzinoms. [Symptomatology and diagnosis of bronchial carcinoma.] *Krebsarzt* 3: 1-19, Jan., 1948.—The author discusses symptomatology and diagnosis of bronchial carcinoma on the basis of 120 patients, of whom 78 were inoperable on clinical examination, 26 inoperable on exploratory thoracotomy, 6 refused operation, and 10 were operable. In 72, 2 wks. to more than 3 yrs. elapsed between appearance of first symptoms and examination; in 41 of these, 6 mos. to 1 yr.—*M. C. J.*
- ### LUNG AND PLEURA
- Bisgard, J. Dewey [Omaha, Nebr.]: Pulmonary cavernous hemangioma with arteriovenous fistula, surgical management: case report. *Ann. Surg.* 126: 965-972, Dec., 1947.
- Brantigan, O. C. [Sch. Med., Univ. Md., Baltimore]: Carcinoma of the lung. A challenge to early diagnosis. *Bull. Sch. Med., Univ. Maryland* 32: 131-139, Jan., 1948.—There is need for greater awareness of the varied symptomatology of lung cancer. There may be no symptoms, when the disease can be picked up only by mass chest x-rays. Distant metastasis from a silent lung primary may be the first sign and pulmonary symptoms never appear in such patients. Others will have had no previous pulmonary symptoms and may have either an insidious onset of chronic lung complaints or an acute pulmonary illness. The third group contains patients with other long-standing lung disease in whom a cancer secondarily develops. Because of such variations in the clinical setting, chest x-rays of healthy adults should be more widely taken; any male more than 35 with a chronic pulmonary complaint should be suspected of cancer; every pulmonary disease should be accurately diagnosed with all laboratory aids; and exploratory thoracotomy should be freely employed as a diagnostic method. Between February, 1943, and January, 1947, the author saw 63 private patients with lung cancer, explored 37, and was able to resect the tumor in 20 (54%), comparable to Oschner's figure of 59.8% in a group of 246 ward and private patients.—*J. L. Pool, M.D.*
- Bruninx, Willy: La bronchoscopie dans les cancers broncho-pulmonaires. [Bronchoscopy in bronchopulmonary cancer.] *Rev. méd. Liège* 2: 514-524, Sept. 15, 1947.—A review of 55 cases; 19 case reports.
- Campbell, Murray H., & Penner, D. W. [Univ. Manitoba, Winnipeg]: Mesothelioma of the pleura. *Canadian M. A. J.* 58: 371-373, Apr., 1948.—Case report.
- De Nicola, Carlos P.: Cáncer de pulmón. Neumonectomía en un carcinoma de pulmón con síndrome de Bamberger-Marie. [Cancer of the lung. Pneumonectomy for cancer of the lung with Bamberger-Marie syndrome.] *Bol. y trab., Acad. argent. de cir.* 31 (31): 1067-1071, 1947.—Case report.
- Desaive, Paul [Univ. Liège, Belg.]: L'exérèse chirurgicale des tumeurs du poumon et du médiastin. [Surgical extirpation of tumors of the lung and mediastinum.] *Rev. méd. Liège* 2: 493-503, Sept. 15, 1947.—A review.
- Effler, Donald B., & Blades, Brian [Washington, D. C.]: Surgical treatment of the solitary lung metastasis. *J. Thoracic Surg.* 17: 27-37, Feb., 1948.—Six cases from the literature and 3 new cases are reported in which solitary pulmonary metastases were resected. The primary cancers were: 4, adenocarcinoma of the large bowel; 1 each, renal adenocarcinoma, uterine adenocarcinoma, testicular chorionepithelioma, liposarcoma of the thigh, and synovium of the calf. The interval between resection of the primary tumor and the metastasis ranged from 2 mos. in Blades' patient with malignant synovium to 13 yrs. in the uterine adenocarcinoma. 6 patients without evidence of cancer are living from 6 mos. to 16 yrs. after pulmonary resection, 3 more than 4 yrs. The malignant synovium in a 23-yr.-old male had been present for 2 yrs. prior to amputation; the specimen showed invasion of the posterior tibial vein. Chest x-ray showed a mass 4 cm. in diameter in the right middle lobe prior to amputation; 17 mos. following lobectomy, there was no evidence of further metastasis.
- One patient died of metastases 9 mos. after pneumonectomy by Raine, the primary rectal lesion having been removed 8 mos. prior to pneumonectomy. One colon patient (Effler's),

whose right upper lobe metastasis was present 9 mos. prior to lobectomy, developed an intracranial metastasis 5 mos. later, also successfully excised, and the patient was well 2 mos. later. The choriocarcinoma case (Effler's) developed a left lower lobe metastasis visible in x-rays 10 mos. after orchiectomy and radical groin and retroperitoneal node dissection, in which regions no metastatic disease had been found. His lobectomy was 17 mos. after the original operation; a hilar node was found in the specimen adherent to the inferior pulmonary vein. Skull and cerebral metastases were evident 4 mos. later. The chance for permanent arrest seems better in slow-growing, and therefore late-appearing, solitary pulmonary metastases.—*J. L. Pool, M.D.*

Evans, T. Islwyn [Church Village, Glam., Wales]: Cancer of the lung. *Brit. M. J.* 1: 474, Mar. 6, 1948.

Gale, J. W., & Curreri, A. R. [Univ. Wis. M. Sch., Madison]: Present status of pulmonary resection for carcinoma and inflammatory diseases of the lung. *Wisconsin M. J.* 47: 210-213, Feb., 1948.

Gordon, Burgess [Jefferson Hosp., Philadelphia, Pa.]: Pulmonary cysts. *Dis. of Chest* 14: 193-197, Mar./Apr., 1948.

Gottlieb, Charles, & Sharlin, Herbert S. [N. Y. Hosp., New York City]: Hilar densities simulating neoplasms. *Radiology* 50: 57-64, Jan., 1948.

Jones, John C. [Los Angeles, Calif.]: California Cancer Commission Studies. Chapter XVI. Carcinoma of the lung. *California Med.* 68: 305-307, Apr., 1948.

Lambert, Adrian [Columbia Univ. & Bellevue Hosp., New York City]: Carcinoma of the lung. *Am. J. M. Sc.* 215: 1-12, Jan., 1948.—Of 349 cases of lung cancer seen on the chest service at Bellevue Hospital, 1939 to Feb. 1946, 279 were deemed inoperable because of distant metastasis (150 histologically proved). Pulmonary and pleural suppuration was considered no contraindication to surgery. 70 patients were explored: in 45, resection was not done, because of mediastinal or chest-wall extension or metastasis not visualized by x-ray. There were 20 pneumonectomies and 5 lobectomies. The patients averaged 52.8 yrs.; all but 2 were male. Symptoms, including weight loss, were parallel in the resected and the explored groups, but the explored more often showed blood, pain, and wheezing, though they came to the hospital 2 mos. sooner than the resected (av. 7 mos. from onset of symptoms). Bronchoscopy was positive in 36 of 63 (57%); 13 were resectable. 7 of 16 with completely negative bronchoscopies were also resectable; this procedure is not believed capable of determining resectability. [No mention is made of histologic study by aspiration biopsy or sputum smear.]

Anatomically, 16 of 43 lesions in the right lung and 9 of 27 in the left were resected.

Pathology: squamous-cell, 11 of 28; undifferentiated carcinoma, 8 of 23; adenocarcinoma, 6 of 8; adeno- and squamous carcinoma, 1; unclassified carcinoma, 10—none resected. The undifferentiated cell cases averaged 2 mos. shorter duration before hospitalization, while the adenocarcinomas were least likely to show a positive bronchoscopic biopsy.

Following surgery, the nonresected patients had a 16% hospital mortality; the resected, 40%, though only 7 of these 10 died in the first mo., a 28% postoperative mortality. Bronchopleural fistula led to death in 3 patients, each dying after the first mo. with recurrence or metastasis. After resection, prognosis was best in the squamous-cell type, the only 5-yr. survival being in this group; and 3 of the 10 cases followed were living more than 24 mos. In the undifferentiated cell group, 3 of 8 lived more than 24 mos., while none of the 3 resected-and-followed adenocarcinoma cases survived 1 yr. Comparable longevity was rare in the non-resected group; only 5 of the 20 followed were living more than 12 mos.; 1 with adenocarcinoma and 1 with squamous carcinoma went over 48 mos. Some of these patients were irradiated, which may have influenced survival.—*J. L. Pool, M.D.*

Leroux, G. F. [Univ. Liège, Belg.]: Le diagnostic du cancer pulmonaire et de ses stades évolutifs. Acquisitions récentes. [Diagnosis of cancer of the lung and of its evolutionary stages. Recent advances.] *Rev. méd. Liège* 2: 504-509, Sept. 15, 1947.

Levitt, Nathan [Harper Hosp., Detroit, Mich.]: Primary carcinoma of the lung. Report of 100 cases. *J. Michigan State M. Soc.* 47: 395-399, Apr., 1948.

Melick, D. W., & Williams, O. O. [Phoenix, Ariz.]: Multiple primary carcinomas. *Arizona Med.* 5: 29-31, Mar., 1948.—Case report: simultaneous carcinomas of terminal alveoli, right lung; main-stem bronchus, left lung; prostate gland.—*D. A. S.*

Moreno, Iván Goñi: Hamartoblastoma del pulmón. [Hamartoblastoma of the lung.] *Bol. y trab., Acad. argent. de cir.* 31 (21): 754-756, 1947.—Case report.

Ochsner, Alton; DeBakey, Michael E., & Dixon, J. Leonard [Sch. Med., Tulane Univ. La., New Orleans]: Primary malignancy of the lung. *South Dakota J. Med. & Pharm.* 1: 43-47, Feb., 1948.

Ochsner, Edward Wm. Alton [New Orleans, La.]: Cancer of the chest cavity. *Kentucky M. J.* 46: 136-138, Apr., 1948.

Pavlovsky, Alejandro J.: Neoplasia pulmonar. [Pulmonary neoplasia.] *Bol. y trab., Acad. argent. de cir.* 31 (30): 1032-1035, 1947.

Ravelli, A. [Univ.-Klin. Innsbruck, Austria]: Zum röntgenologischen Erscheinungsbild metastatischer Lungengeschwülste: ein Fall von Lymphangioma metastaticum rhabdomyosarco-

- matosa. [The roentgenographic appearance of lung tumors: a case of metastatic rhabdomyosarcomatous lymphangitis.] *Krebsarzt* 3: 55-60, Feb., 1948.
- Rogers, William Lister [San Francisco Hosp. Unit, Dept. Pub. Health, Calif.]: Cystic disease of the lungs. *West. J. Surg.* 56: 157-165, Mar., 1948.
- Schiafer, Paul W., & Scott, Orland B. [Univ. Chicago Clin., Chicago, Ill.]: Should solitary pulmonary "metastases" be resected? *J. Thoracic Surg.* 16: 524-529, Oct., 1947.—A case of coincident giant-cell tumor of the right ulna and a hamartoma of the left lung which simulated a metastasis is reported. The value of exploratory thoracotomy is re-emphasized.—*Auth. Summ.*
- Stein, Justin J. [Los Angeles Tumor Inst., Calif.]: Primary cancer of the lung. *Ann. West. Med. & Surg.* 2: 125-127, Mar., 1948.
- Theodos, Peter A. [Jefferson M. Coll. Hosp., Philadelphia, Pa.]: Cystic disease of the lung with report of a case. *Dis. of Chest* 14: 115-120, Jan./Feb., 1948.
- Togni, Giulio [Univ. Pisa, Italy]: In tema di neoplasie maligne pleuriche. [Malignant neoplasm of the pleura.] *Policlinico (sez. chir.)* 54 (11/12): 200-212, 1947.—Case report.
- ## TUMORS OF INFANCY AND CHILDHOOD
- Dargeon, Harold W. [New York City]: Cancer in children. *Kentucky M. J.* 46: 145-146, Apr., 1948.
- Dargeon, Harold W. [Memorial Hosp., New York City]: Cancer in children from birth to fourteen years of age. *J.A.M.A.* 136: 459-468, Feb. 14, 1948.—Statistics of incidence and discussion of tumors occurring at the six most frequently affected sites: bones, kidneys, eye and orbit, lymphatic and blood-forming organs, soft somatic tissues, nervous system.—*D. A. S.*
- Hendrick, J. G. [St. Joseph Hosp., Memphis, Tenn.]: Hemangioma of the liver causing death in a newborn infant. *J. Pediat.* 32: 309-310, Mar., 1948.
- Kenney, John M. [Sonoma, Calif.]: California Cancer Commission Studies. Chapter VII. Childhood cancer. *California Med.* 67: 325-329, Nov., 1947.
- Papierniak, Frank B.; Ayer, John P., & Herbst, Robert H. [Chicago, Ill.]: Large retroperitoneal ganglioneuroma in a child. *Proc. Inst. Mcd. Chicago* 17: 48-49, Feb. 15, 1948.
- Seiler, William C., Jr. [West. Reserve Univ. Sch. Med., Cleveland, Ohio]: Cerebellar medulloblastoma in a seven-month-old infant. *J. Pediat.* 32: 317-319, Mar., 1948.
- Topper, Anne [Mt. Sinai Hosp., New York City]: Basal metabolism of children with tumors. *Am. J. Dis. Children* 74: 669-681, Dec., 1947.—Basal metabolic rates were determined on 21 children with brain tumors and 19 with tumors elsewhere. The metabolic rates in those with brain tumors were all negative, —3 to —21, irrespective of whether the tumors were benign or malignant. The metabolic rate was increased in all 19 with tumors elsewhere; 3, with benign tumors, had a normal metabolic rate of 0 to +12%; 16 had a greatly elevated rate of +27 to +50%; all had highly malignant tumors, including neuroblastoma, sarcoma, lymphosarcoma, carcinoma, and adenocarcinoma. The author suggests that the basal metabolic rate be used in the diagnosis of tumors, e.g., a low metabolic rate associated with unexplained headaches or vomiting should suggest a brain tumor. 2 chest x-rays are shown, each with a shadow in the upper mediastinum: In 1, the metabolic rate was +9; the surgical specimen was a ganglioneuroma. In the other, the rate was +38; at autopsy the tumor proved to be neuroblastoma.—*A. G. James, M.D.*
- Wilensky, A. O. [New York City]: Wilms' tumor. *J. M. Soc. New Jersey* 45: 21-22, Jan., 1948.—Case report.
- ## RESEARCH—GENERAL
- Anon.: Symposium on cancer research. *Texas Rep. Biol. & Med.* 5: 367-382, Winter, 1947.
- Begg, R. W. [Dalhousie Univ., Halifax, N. S.]: Cancer research. *Nova Scotia M. Bull.* 27: 64-71, Mar., 1948.
- Cowdry, E. V. [Wash. Univ., & Barnard Free Skin & Cancer Hosp., St. Louis, Mo.]: Expectations in cancer research. *Proc. Inst. Med. Chicago* 17: 30-38, Feb. 15, 1948.
- Dickie, Annamae, & Hempelmann, Louis H. [Los Alamos Sc. Lab., Los Alamos, N. M.]: Morphologic changes in the lymphocytes of persons exposed to ionizing radiation. *J. Lab. & Clin. Med.* 32: 1045-1059, Sept., 1947.—Analysis of the total leukocyte counts of persons [majority, 20 to 30 yrs. old] chronically exposed to ionizing radiation and toxic chemicals shows a significant statistical decrease in the exposed groups. Analysis of the absolute number and of the percentage of lymphocytes in the differential counts of the same persons shows no significant change. Morphologic study of supravital preparations of blood cells of persons chronically and acutely exposed to ionizing radiation indicates a striking increase in the number of refractive neutral red bodies in the cytoplasm of the circulating lymphocytes. An increase in neutral red bodies is also found in persons working with toxic chemicals. These neutral red bodies have high density and may be considered to be granules. They have not been identified in fixed preparation.—*Auth. Summ.*

Dobrovolskaia-Zavadskaia, N. [Curie Inst., Paris, France]: Life and death phenomena in cancerous cells. *Rocky Mountain M. J.* 45: 298-301, Apr., 1948.

Dunn, Thelma B. [Nat. Cancer Inst., Bethesda, Md.]: Research at the National Cancer Institute. *M. Woman's J.* 55: 15-20, Apr., 1948.

Evans, Virginia J.; Earle, Wilton R.; Schilling, Edward L.; Wilson, Elizabeth P., & Duchesne, Emily [U. S. Pub. Health Serv., Washington, D. C.]: The use of perforated cellophane for the growth of cells in tissue culture. *J. Nat. Cancer Inst.* 8: 103-119, Dec., 1947.

Hieger, I. [Roy. Cancer Hosp., London, Eng.]: Progress of cancer research. *Nature* 161: 385-386, Mar. 13, 1948.

Karnofsky, David A.; Graef, Irving, & Smith, Homer W. [N. Y. Univ. Coll. Med., New York City]: Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo. *Am. J. Path.* 24: 275-291, Mar., 1948.—Methyl-bis (β -chloroethyl) amine hydrochloride ($\text{HN}_2 \cdot \text{HCl}$) was used as the type substance in this study. (Tris β -chloroethyl) amine hydrochloride ($\text{HN}_3 \cdot \text{HCl}$) and bis (β -chloroethyl) sulfide (H) were examined in more limited trials and, in the particulars tested, gave essentially the same results as did $\text{HN}_2 \cdot \text{HCl}$. The "alarm reaction" of Selye must be considered in interpreting the toxic effects of any drug. It is shown that only a minor and questionable role can be ascribed to this reaction in the production of the characteristic pattern of injury to the lymphatic and hematopoietic tissues and intestinal mucosa resulting from $\text{HN}_2 \cdot \text{HCl}$ intoxication. Following the injection of $\text{HN}_2 \cdot \text{HCl}$ in the rat, involution of the lymphatic tissue and lymphocytic destruction occur in the absence of the adrenal glands. That the damage to the intestinal tract and bone marrow is a rapidly completed and presumably direct action of the agent, and is not related to the "alarm reaction," was shown by the following procedures: (a) By occluding the circulation to a portion of the small intestine during and for 5 to 15 min. after the injection of a lethal dose of $\text{HN}_2 \cdot \text{HCl}$, that portion was protected from the damaging effect of the compound. (b) By occluding the circulation to the lower extremities by a clamp on the abdominal aorta and inferior vena cava during and for 2 to 15 min. after the intravenous injection of $\text{HN}_2 \cdot \text{HCl}$, granulocytopenia in the peripheral blood was prevented, and at autopsy hyperplasia of the femoral marrow, with aplasia of the rest of the bone marrow in the body, was observed. Beginning 6 hrs. after the injection of a lethal dose of $\text{HN}_2 \cdot \text{HCl}$ in the rabbit, the growth of hemolytic streptococci in the serum is enhanced. This suggests that an alteration occurs in the blood, making it more favorable for the growth of bacteria.—*Auth. Summ.*

Regalado, Gabriel González: Técnica del cultivo de tejidos de tumores vegetales. [Tech-

nique for tissue culture of vegetable tumors.] *Bol. Liga contra el cáncer* 21: 190-194, Nov./Dec., 1947.

ANIMAL EXPERIMENTATION

Bittner, John J. [Univ. Minn. M. Sch., Minneapolis]: Propagation of the mammary tumor milk agent in tumors from C₃ black mice. *Proc. Soc. Exper. Biol. & Med.* 67: 219-221, Feb., 1948.—Mice of some sublines of the C57 black stock may propagate and transmit the mammary-tumor agent. The agent may be recovered from spontaneous mammary cancers which developed in mice of the strain and may survive for at least 10 passages of these tumors in mice without the agent.—*Auth. Summ.*

Clerch, Antonio [Nat. Inst. Hyg., Cuba]: Inmunidad antivariólica en la evolución del papiloma Shope. [Effect of smallpox vaccination on the development of Shope's papilloma.] *Bol. Liga contra el cáncer* 21: 185-189, Nov./Dec., 1947.

Gross, Ludwik [Veterans Adm. Hosp., Bronx, N. Y.]: Increased hemolytic potency of mouse mammary carcinoma extracts following incubation with tumor cells. *Proc. Soc. Exper. Biol. & Med.* 67: 341-343, Mar., 1948.—If separated from the tumor cells by centrifugation, the mouse mammary-carcinoma extracts lose their hemolytic potency after 5 hrs., when incubated at 37° C. On the other hand, the hemolytic potency of the tumor extracts is either moderately or substantially increased following incubation in presence of tumor cells, at 37° C., for either 5 or 24 hrs. Fresh extracts prepared from normal mouse cells usually have no hemolytic potency, except for those made from active mouse mammary gland. If the normal mouse-cell suspensions (liver, lungs, muscle, or pooled organs), however, are incubated at 37° C. for 5, or better for 24, hrs., some may show a slight hemolytic potency, though to a lesser degree than that observed in the case of pre-incubated tumor-cell suspensions.—*Auth. Summ.*

Lacassagne, A. [Inst. du Radium, Paris, France]: Sur la différence des lésions histologiques produites, dans la peau de la souris, par les radiations ultra-violettes et par les radiations roentgen. [The difference in histologic lesions in the skin of the mouse produced by ultra-violet and x-ray irradiation.] *Acta radiol.* 28: 461-467, Nov., 1947.

Law, L. W.; Bunker, Lester E., Jr., & Norris, Betty-Ann [Roscoe B. Jackson Memorial Lab., Bar Harbor, Me.]: Effect of gonadectomy and adrenalectomy on the appearance and incidence of spontaneous lymphoid leukemia in C58 mice. *J. Nat. Cancer Inst.* 8: 157-159, Dec., 1947.—Orchiectomy of immature males of strain C58 significantly increased the incidence of spontaneous lymphoid leukemia. In this strain, ovariectomy had no apparent effect on leukemia incidence. Adrenalectomy of im-

mature male and female mice of the C58 strain significantly increased the incidence of spontaneous lymphoid leukemia.—*Auth. Summ.*

Li, Min Hsin [Yale Univ. Sch. Med., New Haven, Conn.]: Malignant granulosa-cell tumor in an intrasplenic ovarian graft in a castrated male mouse. *Am. J. Obst. & Gynec.* 55: 316-320, Feb., 1948.

Li, Min Hsin; Gardner, W. U., & Kaplan, Henry S. [Yale Univ. Sch. Med., New Haven, Conn.]: Effects of x-ray irradiation on the development of ovarian tumors in intrasplenic grafts in castrated mice. *J. Nat. Cancer Inst.* 8: 91-98, Dec., 1947.—Granulosa-cell tumors, luteomas, or mixed tumors developed in irradiated (400 r), intrasplenic ovarian grafts in 7 of 9 castrated female mice and in all 8 castrated male mice. The incidence and time of origin of these tumors were not modified by irradiation. Neither ova nor normal ovarian follicles were observed in any of the irradiated grafts. X-ray irradiation of the hypophysis and adjacent tissues (400 r) did not inhibit the formation of the intrasplenic ovarian tumors which developed in 9 of 12 mice so treated. Ovaries irradiated in vitro (200 r) and subsequently grafted into the spleens of castrated hosts gave rise to tumors but with a lower incidence than did grafts irradiated in vivo.—*Auth. Summ.*

Llambés, Juan J. [Inst. Nat. Hyg., Cuba]: La inmunidad anticarcinomatosa en la evolución del papiloma de Shope. [Effect of anti-cancer immunity on the development of Shope's papilloma.] *Bol. Liga contra el cáncer* 21: 181-184, Nov./Dec., 1947.

Miller, J. A., & Miller, E. C. [Univ. Wis., Madison]: The carcinogenicity of certain derivatives of *p*-dimethylaminoazobenzene in the rat. *J. Exper. Med.* 87: 139-156, Feb. 1, 1948.—The previous studies of these authors on the action of *p*-dimethylaminoazobenzene in the production of liver tumors in the rat have been extended to the determination of carcinogenicity of its known and certain possible metabolites, singly, and in various combinations; and to further investigations on the carcinogenic activity of its derivatives obtained by substitution on the amino group or ring positions. In the testing of some 37 derivatives, adult male albino rats of the Sprague-Dawley strain, 150-200 gm. in weight, were used. Most of the tests were done on groups of 12 young rats. Most of these dyes except 4-aminoazobenzene were fed at molar levels equivalent to 0.06% of 4-dimethylaminoazobenzene, mixed in a semisynthetic diet consisting of crude casein, corn oil, rice-bran concentrates, salt mixture, and glucose monohydrate. The compound was fed from 4 to 7 mos. depending on its activity. Usually at the end of the dye-feeding period the livers were examined by laparotomy and the rats were then fed the same diet without the test compounds for an additional 2 mos. Of the 18 known or possible metabolites of 4-dimethylaminoazobenzene, only the 4-monomethylamino-

zene, a known metabolite, was active. 8 compounds that appear to be metabolites of the dye, as well as 9 that may possibly be, were inactive. A mixture of 9 known and possible metabolites was also found to be inactive. These data indicated that the primary carcinogen operative in tumor formation by 4-dimethylaminoazobenzene is probably an azo dye closely related to the parent carcinogen. This conclusion is supported by previous work by these authors which indicated that the primary carcinogen consisted of either or both of the protein-bound dyes found in the liver—4-monomethylaminoazobenzene and an unidentified polar amino azo dye—and that the formation of bound dye constitutes one of the first steps in this carcinogenic process. The carcinogenic activities of 19 other compounds related to 4-dimethylaminoazobenzene were tested to obtain more information on the structural features needed for strong activity in the rat. 3'-methyl-4-monomethylaminoazobenzene and the corresponding dimethylamino derivative were nearly twice as active and the 4-ethylmethylaminoazobenzene had the same activity as 4-dimethylaminoazobenzene. As tested, 3'-nitro- and 3'-chloro-4-dimethylaminoazobenzene both had about the same activity as the parent compound. However, since the 3'-nitro derivative was incompletely absorbed, its real activity appeared to be about 1½ times that of 4-dimethylaminoazobenzene. The data on the carcinogenicity of the 2', 3', or 4'-methyl, chloro, and nitro derivatives of 4-dimethylaminoazobenzene show that the position of these groups determines the carcinogenicity of these compounds to a greater extent than does the type of group. The activity relationship was: 3' > 2' > 4'. From the available data, two conditions appear to be essential if a dye is to possess high activity: (1) at least one methyl group must be attached to the amino group together with a proper second substituent, and (2) the rings must bear either no substituents or carry only certain substituents, preferably in the 3' position. The preparation of several new derivatives of *p*-dimethylaminoazobenzene is described.—*J. H. Burchenal, M.D.*

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- In vitro, a concentration of 0.0026 M of H will produce an immediate inhibition in bone-marrow glycolysis of about 60%. The serum of rabbits poisoned with intravenous doses of H up to 25 mg./Kg. ($5 \times$ a lethal dose) and obtained 1 to 21 hrs. after injection, did not inhibit bone marrow glycolysis in vitro. Extracts of fat from poisoned rabbits, which conceivably might contain reservoirs of unchanged H, did not inhibit bone-marrow glycolysis. It therefore appeared paradoxical that the temporary occlusion of the blood circulation to the hind legs of rats for 20 to 60 mins. after the intravenous injection of a lethal dose of H (2 mg./Kg.) failed to protect the femoral marrow. This observation suggested that a substance injurious to the bone marrow was present in the blood in vivo at least one hour after the injection of H, although this could not be shown by the in vitro studies.
- [In the case of a water-soluble nitrogen mustard (methyl-bis $[\beta$ -chloroethyl] amine hydrochloride), occlusion of the circulation to the extremities of the rat and rabbit for 2 to 10 mins. during and after the injection of the agent, was shown to protect the femoral marrow (Karnofsky, D. A., Graef, I., and Smith H. W.: Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo. *Am. J. Path.* 24: 275-291, 1948). Under similar circumstances the femoral marrow in both the rabbit and rat was protected at doses of H near the LD₅₀. At a higher dose of H in the rat, the protection of the femoral marrow was not found, which is in keeping with the observations of Needham, *et al.* The anomalous result with high doses of H in the rat is unexplained.]—*D. A. Karnofsky, M.D.*
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occur in mouse epidermis during the precancerous stages of epidermal carcinogenesis. The mean value for the adenylypyrophosphatase activity of tumors was 3 times that observed for normal epidermis on a wet-weight basis and approximately 6.5 times on a dry-weight basis. The findings are discussed in relation to the values reported previously for cytochrome oxidase and succinic dehydrogenase in epidermal carcinogenesis and are compared to results obtained for normal liver and hepatomas.—*Auth. Summ.*

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CARCINOMA OF THE BREAST

Recurrence and Survival in 203 Patients

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THROUGH the past fifty years, an enormous volume of fact and theory concerning the treatment of carcinoma of the breast has accumulated in the medical literature. Unfortunately, reported series have contained widely varied results and diverse conclusions regarding specific forms of therapy, so that unanimity of opinion between accepted authorities is lacking. The confusion and conflict of belief is wholly due to the lack of a universally accepted, reliable classification of the different types and stages of carcinoma of the breast. It is almost impossible, at the present time, to find two large series of cases from different sources that use an identical system of classification. Until this goal can be reached, the confusion of fact and belief will persist.

This report is a statistical study of the five-, seven-, and ten-year-survival rates of 203 consecutive cases of carcinoma of the breast in women who were treated surgically, some with and some without supplementary postoperative roentgen therapy. Each case has been carefully evaluated and classified, and the specification of each classification clearly outlined. So-called "Paget's cancer" of the breast has not been included. Secondary facts gleaned from the case histories have been compiled to aid in evaluating factors influencing the prognosis. Recurrence rates are presented.

AGE INCIDENCE

Of the patients, 10.3 per cent were between the ages of 20 and 40 years; 58.1 per cent were between 40 and 60, and 31.6 per cent were more than 60 years of age.

On the basis of population figures pub-

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Received for publication, February 21, 1950.

lished by the Department of Commerce¹² for 1940, it is estimated that, of the female population older than 20 years, 49 per cent were between the ages of 20 and 40, roughly 41.0 per cent were between 40 and 64, and 10 per cent were more than 60 years.

When the figures of Table 1 and Table 2 are presented graphically, the relation of the two curves, in agreement with the belief of Nathanson and Welch, suggests a gradually increasing incidence of carcinoma of the breast with increase of age (Fig. 1).

FAMILIAL HISTORY

Unfortunately, the familial history of cancer did not specify the location of the neoplasm in all cases. Only 24.6 per cent of the patients were aware of malignant tumor in blood relatives.

TABLE 1
AGE INCIDENCE OF CARCINOMA
OF THE BREAST

<i>Age group</i>	<i>Number</i>	<i>Per cent of total (203)</i>
20-29	1	0.5
30-39	20	9.8
40-49	58	28.5
50-59	60	29.6
60-69	45	22.2
70-80	19	9.4
TOTAL	203	100.0

TABLE 2
FEMALE POPULATION U.S.A. 1940¹²

<i>Age group</i>	<i>Number</i>	<i>Approximate percentage</i>
20-29	11,541,419	27.0
30-39	9,971,794	22.0
40-44	4,368,708	10.0
45-54	7,550,052	18.0
55-64	5,163,025	13.0
65-74	3,209,134	8.0
75-	1,404,606	2.0

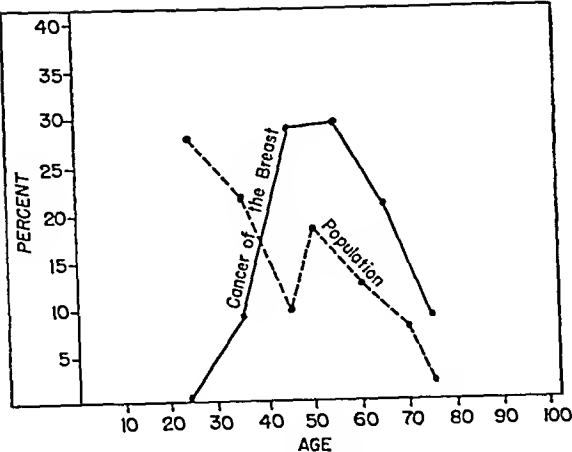


FIG. 1. Age distribution.

FERTILITY

Of the patients, 51.1 per cent had had one or more pregnancies.

SYMPTOMS

The presenting symptom in the majority of cases (67.0 per cent) was the single complaint of a painless mass in the breast. Associated with the mass in 27.9 per cent was pain, usually mild and intermittent. Discharge from the nipple was infrequent, occurring in only 4.6 per cent, and usually noted as a few drops of pinkish-yellow fluid. Pain as a single presenting symptom was rare (0.5 per cent). Six of the 203 cases were discovered at the time of examination for unrelated complaints.

LOCATION OF THE MASS

The location of the mass was roughly the same in the two breasts, with the incidence as given in Table 3. Simultaneously noted bilateral carcinoma occurred in five cases (2.4 per cent). The relation between survival and location will be discussed subsequently.

CLASSIFICATION

To evaluate the success of different forms of therapy in carcinoma of the breast, both a relative and an absolute standard must

be used. The relative standard is used when the results of different forms of therapy are compared.

Unfortunately, comparison of different forms of therapy has resulted in conflicting claims and beliefs. This is due in large measure to the failure to designate clearly the extent of the disease in the cases treated and to segregate cases according to the extent of the disease when the therapy was applied. The results of a series composed of cases treated early in the disease cannot be used to evaluate a mode of therapy used in a series composed of moderately or far-advanced disease. To overcome this problem, a satisfactory classification with a consistent degree of prognostic accuracy must be used.

It is generally conceded that the most important prognostic determinant, omitting remote metastases, is the extent of lymph-node involvement. Second to this are: (1) cutaneous involvement; (2) the degree of local fixation of tumor to the chest wall; (3) the type of carcinoma present as determined by the pathologist.

The various classifications to further prognostic accuracy and to provide a satisfactory basis for study of results of therapy are founded upon these factors. None of the classifications currently in use is completely satisfactory.

Steinthal Classification. The Steinthal classification depends principally upon a clinical estimate of the degree of axillary lymph-node involvement. Taylor and Bruce, in a careful study, have found a discrepancy of 28 per cent between clinical

TABLE 3
LOCATION OF MASS

	% Right breast (47.5%)	% Left breast (52.5%)
Lateral quadrants	28.4	31.4
Upper	25.4	27.4
Lower	3.0	4.0
Medial quadrants	11.7	14.2
Upper	9.8	9.3
Lower	1.9	4.9
Central	7.4	6.9

estimate and pathological finding of axillary metastases. Others have stated that the presence of axillary metastases can be detected clinically in only 50 per cent of the cases,⁹ hence, variation in reported results that utilized this classification is readily understood.

Portmann Classification. In an effort to exclude this inaccuracy, Portmann proposed a combined clinical-pathological classification utilizing, as one of the major criteria, the degree of axillary lymph-node involvement determined by microscopic examination of all lymph nodes obtained. Nevertheless, prognostic inaccuracies and conflicting results occur with this improved classification.

In explanation of these inaccuracies, the work of Saphir is of importance. In serial-section restudy of thirty cases in which axillary lymph nodes had been reported as uninvolved on routine microscopic examination, he found that 33.3 per cent contained carcinoma cells. Furthermore, and most often overlooked, has been the factor of involvement of the internal mammary lymph nodes. In a study of five cases, Handley and Thackray found that in two cases with involvement of the axillary nodes, there was also involvement of the internal mammary nodes; in two cases the axillary nodes were uninvolved but internal mammary nodes contained metastatic carcinoma; and, in one case, there was no lymph-node involvement.

The use of a classification based solely upon the pathological character of the neoplasm suffers from the lack of general agreement among pathologists as to definition of the different types² and grades, the tendency of several types to coexist, and the factors noted in the preceding paragraphs.

Classification by Mode of Treatment. In addition to showing survival figures as a whole for each group (Portmann classification) and type (pathological classification), there has been further subdivision to show survival for those treated by surgery alone and those treated by surgery and immediate

postoperative roentgen-ray therapy. Some of the divisions are too few in numerical content to be statistically conclusive; however, the results obtained permit analysis and conclusions within the limits of factual probability.

Columns of figures often fail to create a definite, lasting impression; therefore, graphic representations have been prepared. In these representations, survival is graphed as a band created by a line of maximum survival and a line of minimum survival.

The figure of minimum survival is the per cent of the *total treated* known to be alive. Since some of the patients are known to have died of unrelated causes, have been lost, or have been operative deaths, a figure of maximum survival has been reached by deducting these cases from the total treated, obtaining the "net treated" and calculating the per cent of the net treated known to be alive.

NATURAL COURSE OF THE DISEASE

The most absolute criterion of the success of treatment of any disease depends upon the mathematical relation between the survival of treated patients and the survival of untreated patients. A table of the natural course of the disease adapted from the work of Daland has been used, forming a basis of comparison on each survival graph. Of a total of 100 cases, Daland found the average duration of life from time of the initial symptom to be forty and a half months and the mean duration of

TABLE 4
NATURAL COURSE OF THE DISEASE¹
100 Cases

<i>Year from first symptom</i>	<i>% Survival</i>
1	79
2	60
3	40
4	30
5	18
6	10
7	5
10	5
13	0

TABLE 5
OVER-ALL SURVEY

	No	% Total	% Net
<i>Cases Followed Min of 5 Yrs</i>			
Total cases treated	203	100.0	
Operative deaths	4	2.0	
Lost	22	10.8	
Dead, unrelated causes	15	7.4	
Net cases followed 5 yrs	162	79.8	100.0
Dead of disease	75	32.1	46.3
Alive	87	47.7	53.7
<i>Cases Followed Min of 7 Yrs.</i>			
Total cases treated	149	100.0	
Operative deaths	23	2.0	
Lost	21	14.1	
Dead, unrelated causes	11	7.4	
Net cases followed 7 yrs	114	76.5	100.0
Dead of disease	65	43.6	57.0
Alive	49	32.9	43.0
<i>Cases Followed Min of 10 Yrs</i>			
Total cases treated	90	100.0	
Operative deaths	2	2.2	
Lost	12	13.3	
Dead, unrelated causes	7	7.8	
Net cases followed 10 yrs	69	76.7	100.0
Dead of cancer	45	50.0	65.2
Alive	24	26.7	34.8

the disease (50 per cent alive and 50 per cent dead), thirty months. This is confirmed by the work of Wade, whose figure for the mean duration of life from the time of first symptom is thirty-two and six-tenths months.

SURVIVAL RATES

The 203 cases, analyzed as a whole, yield Table 5 and Fig. 2.

The five-year-survival rate as demonstrated in the over-all survey is between

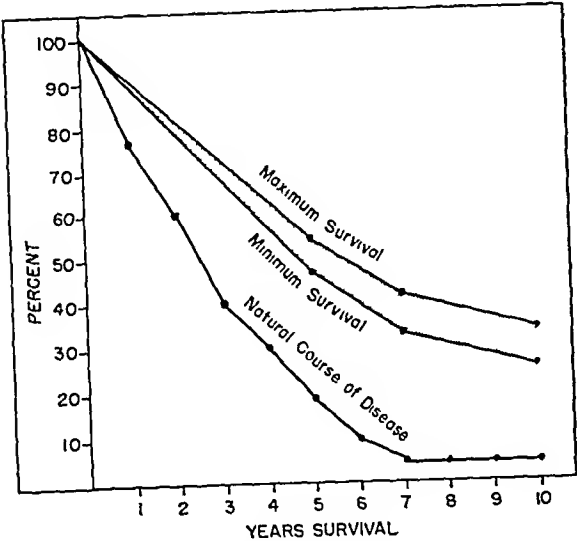


FIG. 2. "Over-all" survey (203 cases).

47.7 and 53.7 per cent, the seven-year-, between 32.9 and 43.0 per cent; and the ten-year-, between 26.7 and 34.8 per cent. Between the fifth and tenth year, the mortality rate in this series has been demonstrated to increase by approximately 20 per cent. The fallacy of the "cures" reported on the basis of a five-year study is clearly indicated.

Survival by Groups (Portmann Classification). The 203 cases have been subdivided into groups I, II, III, and IV, utilizing the Portmann classification, and these groups have been subdivided into those that were treated surgically and those that were treated by surgery supplemented with post-operative roentgen-ray therapy.

The method of grouping according to the Portmann classification is:

Group I

- Skin: Not involved
- Tumor: Localized in breast and movable.
- Metastases: None in axillary nodes or elsewhere.

Group II

- Skin: Not involved.
- Tumor: Localized in breast and movable.
- Metastases: Few axillary nodes involved (less than five in this series), no other metastases.

Group III

- Skin: Edematous, brawny, red, with induration not obviously due to infection; extensive ulceration; multiple secondary nodules.
- Tumor: Diffusely infiltrating breast, fixation of tumor or breast to chest wall; edema of breast, secondary tumor.
- Metastases: Many axillary lymph nodes involved or fixed; no clinical or roentgenological evidences of distant metastases.

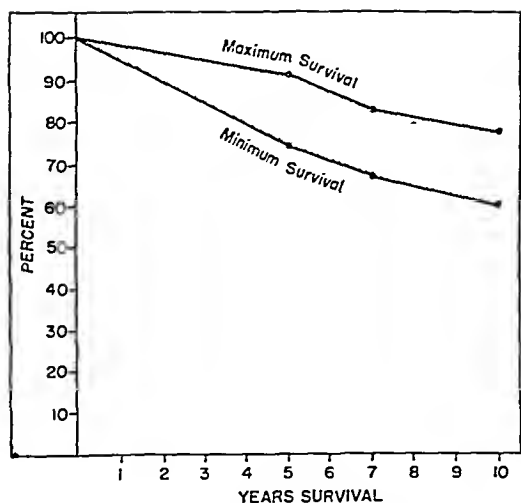


FIG. 3. Group I, all cases (fifty-nine).

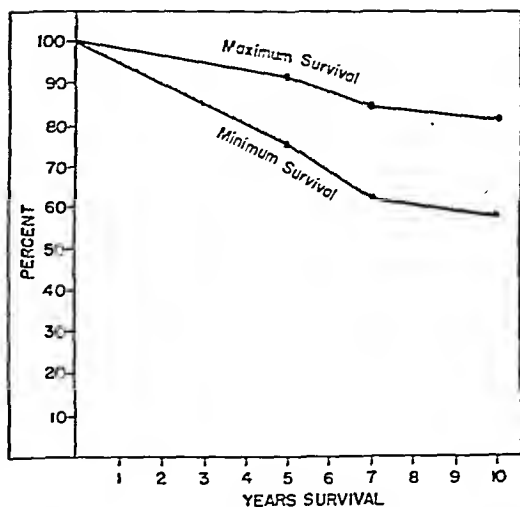


FIG. 4. Group I, surgery only (fifty-two cases).

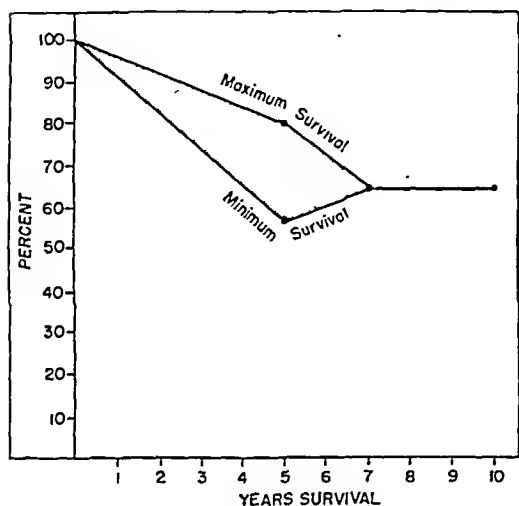


FIG. 5. Group I, surgery and roentgen-ray therapy (seven cases).

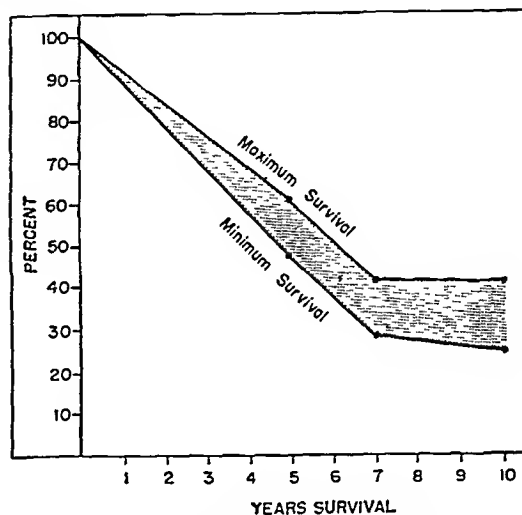


FIG. 6. Group II, all cases (seventy-one).

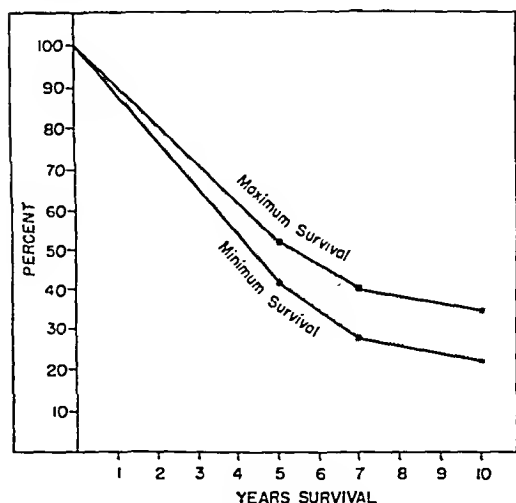


FIG. 7. Group II, surgery only (fifty-six cases).

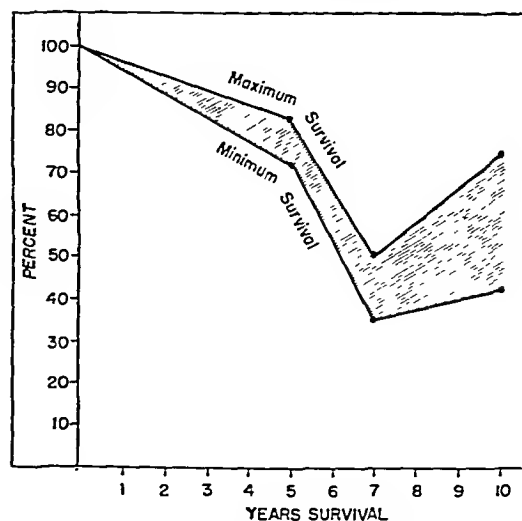


FIG. 8. Group II, surgery and roentgen-ray therapy (fifteen cases).

Group IV

- Skin: As in any other group.
- Tumor: As in any other group.
- Metastases: Axillary and supraclavicular lymph nodes extensively involved and clinical or roentgenological evidences of more distant metastases.

Under this classification, the 203 cases are distributed as in Table 6.

TABLE 6
CLASSIFICATION OF CASES
Portmann Criteria

Group	Number	Per cent
I	59	29.1
II	71	34.9
III	70	34.5
IV	3	1.5
TOTAL	203	100.0

Group I. (See Table 7, Group I.) Of the four group-I cases dead of the disease in five years, medullary carcinoma was found in three and carcinoma simplex in one. Five of the cases followed for seven years died, two of scirrhous, two of medul-

lary, and one of carcinoma simplex; and of the four dead in the group followed for ten years, two died of scirrhous, and two of medullary carcinoma. The distribution of the pathological type among the group-I cases dead of the disease does not clarify the influence of type of carcinoma upon survival.

It is in the group-I cases that 100.0 per cent survival or cure should be realized. By definition, the disease is localized to the breast without axillary-node involvement, yet the mortality over a five-year period is 6.8 to 8.3 per cent. Several explanations must be considered.

1. Undetected axillary-node involvement might have existed. This error could be corrected through the use of serial sections of the axillary nodes as indicated by Saphir's work, with conversion of some of group I to group II or group III.

2. Metastases might have involved the internal mammary or supraclavicular nodes without concomitant or prior involvement of axillary nodes as noted by Handley et al.^{4, 5}

3. Remote metastases via vascular emboli might have been undetected.

4. Radical mastectomy might have been inadequate.

TABLE 7
FIVE-, SEVEN-, AND TEN-YEAR RESULTS IN PORTMANN-GROUPS I, II, AND III

Group and Number	All cases			Operation only			Operation & postop. x-rays		
	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net
Group I (59)									
5-Year results									
Total number treated	59	100.0		52	100.0		7	100.0	
Operative deaths	2	3.4		2	3.8		0	0.0	
Lost	5	8.5		4	7.8		1	14.3	
Dead, unrelated causes	4	6.8		3	5.8		1	14.3	
Net followed 5 yrs.	48	81.3	100.0	43	82.6	100.0	5	71.4	100.0
Dead of disease	4	6.8	8.3	3	5.8	6.9	1	14.3	20.0
Alive	44	74.5	91.7	40	76.8	93.1	4	57.1	80.0
7-Year results									
Total number treated	46	100.0		43	100.0		3	100.0	
Operative deaths	2	4.3		2	4.7		0	0.0	
Lost	8	8.6		3	6.9		0	0.0	
Dead, unrelated causes	3	6.5		8	18.7		0	0.0	
Net followed 7 yrs.	33	80.6	100.0	29	69.7	100.0	3	100.0	100.0
Dead of disease	5	10.8	15.2	4	9.4	13.7	1	33.3	33.3
Alive	28	69.8	84.8	26	60.3	86.3	2	66.7	66.7

TABLE 7—Continued

FIVE-, SEVEN-, AND TEN-YEAR RESULTS IN PORTMANN-GROUPS I, II, AND III

Group and Number	All cases			Operation only			Operation & postop. x-rays		
	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net
<i>10-Year results</i>									
Total number treated	25	100.0		22	100.0		3	100.0	
Operative deaths	1	4.0		1	4.5		0	0.0	
Lost	4	16.0		4	18.0		0	0.0	
Dead, unrelated causes	1	4.0		1	4.5		0	0.0	
Net followed 10 yrs.	19	76.0	100.0	16	73.0	100.0	3	100.0	100.0
Dead of disease	4	16.0	21.1	3	13.6	18.7	1	33.3	33.3
Alive	15	60.0	78.9	13	59.4	81.3	2	66.7	66.7
<i>Group II (71)</i>									
<i>5-Year results</i>									
Total number treated	71	100.0		56	100.0		15	100.0	
Operative deaths	1	1.4		1	1.8		0	0.0	
Lost	9	12.7		7	12.5		2	13.3	
Dead, unrelated causes	5	7.0		5	8.9		0	0.0	
Net followed 5 yrs.	56	78.9	100.0	43	76.8	100.0	13	86.7	100.0
Dead of disease	22	30.9	39.3	20	35.7	46.5	2	13.3	15.4
Alive	34	48.0	60.7	23	41.1	53.5	11	73.4	84.6
<i>7-Year results</i>									
Total number treated	54	100.0		43	100.0		11	100.0	
Operative deaths	1	1.8		1	2.3		0	0.0	
Lost	10	18.5		7	16.3		3	27.2	
Dead, unrelated causes	5	9.3		5	11.6		0	0.0	
Net followed 7 yrs.	38	70.4	100.0	30	69.8	100.0	8	72.8	100.0
Dead of disease	22	40.7	57.8	18	41.8	60.0	4	36.3	50.0
Alive	16	29.7	42.2	12	28.0	40.0	4	36.5	50.0
<i>10-Year results</i>									
Total number treated	32	100.0		25	100.0		7	100.0	
Operative deaths	1	3.1		1	4.0		0	0.0	
Lost	6	18.8		3	12.0		3	42.9	
Dead, unrelated causes	3	9.3		3	12.0		0	0.0	
Net followed 10 yrs.	22	68.8	100.0	18	72.0	100.0	4	57.1	100.0
Dead of disease	13	43.7	59.0	12	48.0	66.7	1	14.3	25.0
Alive	9	25.1	41.0	6	24.0	33.3	3	42.8	75.0
<i>Group III (70)</i>									
<i>5-Year results</i>									
Total number treated	70	100.0		41	100.0		29	100.0	
Operative deaths	1	1.5		1	2.4		0	0.0	
Lost	7	10.0		5	12.2		2	6.9	
Dead, unrelated causes	6	8.5		4	9.8		2	6.9	
Net followed 5 yrs.	56	80.0	100.0	31	75.6	100.0	25	86.2	100.0
Dead of disease	47	67.1	83.9	25	60.9	80.6	22	75.9	88.0
Alive	9	12.9	16.1	6	14.7	19.4	3	10.3	12.0
<i>7-Year results</i>									
Total number treated	48	100.0		30	100.0		18	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	3	6.2		3	10.0		0	0.0	
Dead, unrelated causes	3	6.2		2	6.7		1	5.6	
Net followed 7 yrs.	42	87.6	100.0	25	83.3	100.0	17	94.4	100.0
Dead of disease	37	77.1	88.1	23	76.6	92.0	14	77.8	82.4
Alive	5	10.5	11.9	2	6.7	8.0	3	16.6	17.6
<i>10-Year results</i>									
Total number treated	32	100.0		20	100.0		12	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	2	6.2		2	10.0		0	0.0	
Dead, unrelated causes	3	9.5		2	10.0		0	8.3	
Net followed 10 yrs.	27	84.3	100.0	16	80.0	100.0	11	91.7	100.0
Dead of disease	27	84.3	100.0	16	80.0	100.0	11	91.7	100.0
Alive	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0

Since only seven of this group were recipients of postoperative roentgen-ray therapy, no conclusion can be drawn as to its value.

Group II. (See Table 7, Group II.) With the primary tumor localized in the breast and movable, with secondary neoplasm detected in less than five axillary nodes by microscopic study, and with technically sound surgical treatment, it is astonishing to note a decline in the five-, seven-, and ten-year survivals of the magnitude perceived when group-I and group-II graphs are compared. The explanation of this survival decline clearly indicates that in the group-II cases, the extent of the disease as regards spread to lymphatics other than the axillary, dissemination to remote parts, or microscopically undetected axillary-node involvement is greater than suggested by the clinical and pathological studies. Certainly, one must again question the adequacy of the accepted radical mastectomy as it is conventionally performed.

With only fifteen of the seventy-one cases treated by postoperative roentgen-ray therapy and with two of these lost for five-year, three for seven-year, and three for ten-year evaluation, the results are not statistically significant, although the trend of the curve of survival suggests that postoperative treatment is of value in those cases of group II. The five-year-minimum survival of those treated surgically with supplemental postoperative roentgen-ray therapy is 32.3 per cent greater than those treated with surgical therapy only, the seven-year-minimum survival 8.5 per cent greater, and the ten-year-minimum survival, 18.8 per cent greater.

Group III. (See Table 7, Group III.) Postoperative roentgen-ray therapy administered to twenty-nine of the seventy cases in this group failed to improve the ten-year survival but suggestively improved the maximum seven-year survival by 9.6 per cent. Balancing this apparent benefit of roentgen-ray therapy in the patients traced seven years is a 7.4 per cent greater maximum survival of patients treated with oper-

TABLE 8
YEARLY SURVIVAL OF GROUP-III CASES FOLLOWED FIVE YEARS

	All cases		Operation only		Operation x-rays	
	No.	%	No.	%	No.	%
Total	56	100.0	31	100.0	25	100.0
Survived						
1 yr.	44	78.5	25	80.6	19	76.0
2 yr.	33	58.9	20	64.5	13	52.0
3 yr.	20	35.7	11	35.4	9	36.0
4 yr.	14	25.0	6	19.6	8	32.0
5 yr.	10	17.8	6	19.6	4	16.0
.....						
Cases not incl.						
Operative deaths	1		1		0	
Lost	7		5		2	
Dead, other cause	6		4		2	

ation alone in the group followed five years. Hence, it is difficult to accept as conclusive the benefit of postoperative roentgen-ray therapy in this group. (Table 7, Group III.)

The results obtained with the group-III cases merited further, more detailed, comparison with the natural course of the disease. A year-by-year study (Table 8) for the cases followed for five years is graphically presented and demonstrates with clarity the futility of the surgical and the surgical-plus-roentgen-ray therapy that was used.

Group IV. Group IV included only three cases, of which one could not be traced. All were treated by operation and postoperative roentgen-ray therapy. None survived a five-year period.

This group includes those cases with known remote metastases present at the time of treatment. Unquestionably, it should be much larger, for in it should fall many of the group-II and group-III cases in which remote metastatic disease must have been present at the time of surgery. These unsuspected remote metastases might have been detected through the use of screening roentgenograms of bone and chest, but such a procedure is still not economically feasible and would certainly fail to demonstrate an ultimately lethal but still microscopic nidus of neoplasm.

CLASSIFICATION BY PATHOLOGICAL TYPE

Study of cancer of the breast on the basis of the pathological type present, whether

the study is based on summation of the characteristics of the individual cells, upon the architectural arrangement of the cells, upon the degree of fibrosis and tissue reaction to the neoplasm, or upon a combination of these factors, results in variations in reported results. This is due to the individual differences in interpretation and evaluation of the specimens examined.

TABLE 9

DISTRIBUTION AND FIVE-YEAR
EVALUATION BY PATHOLOGICAL
TYPE

Type	No	%	Net no followed 5 yrs	% Dead	% Alive
Scirrhus	63	31.0	48	51.7	48.3
Simplex	67	33.0	54	50.0	50.0
Medullary	39	19.2	39	51.3	48.7
Adeno-	32	15.8	32	44.0	56.0
Coil gland	1	0.5			
Unclassified*	1	0.5			
TOTAL	203	100.0			

* Primary removed elsewhere but axillary nodes contained secondary neoplasm

In this series, different architectural groupings of neoplastic cells could be repeatedly demonstrated in the same or different sections from a single lesion. Though the method may be subject to just criticism, the individual lesions have been classified here according to the most dedifferentiated architectural type discovered in the study of each lesion. The order of malignancy has been assumed to be: scirrhus, simplex, medullary, adeno-, mucinous, intraduct, and coil-gland. Intraduct and mucinous carcinomas were not encountered in this series, the absence of the former perhaps being due to the omission of all cases of Paget's disease.

SURVIVAL BY PATHOLOGICAL TYPE

Over a five-year-postoperative period, the cases have been grouped by pathological type. The cases lost because of operative death, those that could not be traced, and those known to have died of unrelated causes have been eliminated. The survival percentages then have been calculated upon the net followed five years, and represent the maximum-survival rates.

The results portrayed in Table 9 reveal no significant difference in maximum five-year survival of the commonest pathological types with the method of classification used. Mucinous, intraduct, and coil-gland types could not be evaluated because of their small number or absence from the series.

A further subdivision of the pathological types has been made upon the basis of the Portmann classification (Table 10).

In the scirrhus type, the five-year group I minimum survival is 73.4 per cent, the group-III is 14.3 per cent. This is roughly paralleled in the other groups for the five-, seven-, and ten-year studies. From this must be concluded that survival is primarily dependent upon the extent of the lesion and may be modified only to a lesser degree by the pathological type of lesion present, as determined by methods used in this series and in so far as scirrhus, simplex, medullary, and adenocarcinoma are concerned.

Duration and Survival. Duration of the disease (Table 11) prior to treatment is based upon the patient's estimate of the time of appearance of the first symptom.

The method of determining duration is grossly inaccurate for each individual case, but, in comparing these two groups, a crude index is available.

Over-all survival in those cases treated within six months of the appearance of the initial symptom bettered by almost 13.0 per cent the survival of the cases treated more than a year after the noted onset of the disease. It is surprising that the difference is not greater, and this suggests a slow distal spread of the disease.

The relation of duration to extent of the disease is manifest by the ratio of groups I and II to groups III and IV in the two time units. In the time unit "under six months," groups I and II include a total of 73.8 per cent of the cases, whereas, in the time unit "over twelve months," groups I and II account for only 49.0 per cent of the total cases. The equivalence of the survival rates in similar groups in each of the time

TABLE 10

FIVE-, SEVEN-, AND TEN-YEAR RESULTS IN SCIRRHOUS, SIMPLEX, MEDULLARY,
AND ADENOCARCINOMA

<i>Type of Carcinoma</i>	<i>Group I</i>			<i>Group II</i>			<i>Group III</i>		
	<i>Total no.</i>	<i>% Of total</i>	<i>% Of net</i>	<i>Total no.</i>	<i>% Of total</i>	<i>% Of net</i>	<i>Total no.</i>	<i>% Of total</i>	<i>% Of net</i>
<i>Scirrhus Carcinoma* (61)</i>									
<i>5-Year results</i>									
Total treated	15	100.0		18	100.0		28	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	2	13.3		3	16.7		2	7.1	
Dead, unrelated causes	2	13.3		3	16.7		3	10.8	
Net followed 5 yrs.	11	73.4	100.0	12	66.6	100.0	23	82.1	100.0
Dead of disease	0	0.0	0.0	4	22.2	33.3	19	67.8	82.6
Alive	11	73.4	100.0	8	44.4	66.7	4	14.3	17.4
<i>7-Year results</i>									
Total treated	13	100.0		12	100.0		15	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	2	15.4		3	25.0		1	6.6	
Dead, unrelated causes	2	15.4		3	25.0		1	6.6	
Net followed 7 yrs.	9	69.2	100.0	6	50.0	100.0	13	86.8	100.0
Dead of disease	2	15.4	22.2	2	16.7	33.3	11	73.6	84.6
Alive	7	53.8	77.8	4	33.3	66.7	2	13.2	15.4
<i>10-Year results</i>									
Total treated	6	100.0		6	100.0		12	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	1	16.6		2	33.3		1	8.3	
Dead, unrelated causes	0	0.0		0	0.0		1	8.3	
Net followed 10 yrs.	5	84.4	100.0	4	66.7	100.0	10	83.4	100.0
Dead of disease	2	33.3	40.0	3	50.0	75.0	10	83.4	100.0
Alive	3	51.1	60.0	1	16.6	55.0	0	0.0	0.0
<i>Carcinoma Simplex† (67)</i>									
<i>5-Year results</i>									
Total treated	18	100.0		24	100.0		24	100.0	
Operative deaths	0	0.0		1	4.1		1	4.1	
Lost	1	5.5		3	12.5		3	12.5	
Dead, unrelated causes	0	0.0		2	8.4		1	4.1	
Net followed 5 yrs.	17	94.5	100.0	18	75.0	100.0	19	79.3	100.0
Dead of disease	1	5.5	5.8	9	37.5	50.0	17	70.9	89.5
Alive	16	89.0	94.2	9	37.5	50.0	2	8.4	10.5
<i>7-Year results</i>									
Total treated	11	100.0		17	100.0		16	100.0	
Operative deaths	0	0.0		1	5.9		0	0.0	
Lost	2	18.9		4	23.6		0	0.0	
Dead, unrelated causes	0	0.0		2	11.8		1	6.3	
Net followed 7 yrs.	9	81.1	100.0	10	58.7	100.0	15	93.7	100.0
Dead of disease	1	9.5	11.1	5	29.35	50.0	13	81.1	86.7
Alive	8	71.6	88.9	5	29.35	50.0	2	12.6	13.3
<i>10-Year results</i>									
Total treated	6	100.0		12	100.0		11	100.0	
Operative deaths	0	0.0		1	8.3		0	0.0	
Lost	1	16.6		3	25.0		0	0.0	
Dead, unrelated causes	0	0.0		2	16.7		1	9.1	
Net followed 10 yrs.	5	83.4	100.0	6	50.0	100.0	10	90.9	100.0
Dead of disease	0	0.0	0.0	1	8.3	16.6	10	90.9	100.0
Alive	5	83.4	100.0	5	41.7	83.4	0	0.0	0.0

* Group IV included two cases; dead within three years.

† Group IV included 1 case, lost at the end of two years.

TABLE 10—Continued

FIVE-, SEVEN-, AND TEN-YEAR RESULTS IN SCIRRHOUS, SIMPLEX, MEDULLARY,
AND ADENOCARCINOMA

Type of Carcinoma	Group I			Group II			Group III		
	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net	Total no.	% Of total	% Of net
<i>Medullary Carcinoma (39)</i>									
<i>5-Year results</i>									
Total treated	19	100.0		13	100.0		7	100.0	
Operative deaths	2	10.5		0	0.0		0	0.0	
Lost	0	0.0		2	15.3		1	14.2	
Dead, unrelated causes	1	5.3		0	0.0		0	0.0	
Net followed 5 yrs.	16	84.2	100.0	11.0	84.7	100.0	6	85.8	100.0
Dead of disease	3	15.9	18.7	5	30.7	45.4	6	85.8	100.0
Alive	13	68.3	81.3	6	54.0	54.6	0	0.0	0.0
<i>7-Year results</i>									
Total treated	14	100.0		8	100.0		3	100.0	
Operative deaths	2	14.2		0	0.0		0	0.0	
Lost	2	14.2		0	0.0		0	0.0	
Dead, unrelated causes	0	0.0		0	0.0		0	0.0	
Net followed 7 yrs.	10	71.6	100.0	8	100.0	100.0	3	100.0	100.0
Dead of disease	1	7.1	10.0	5	62.5	62.5	3	100.0	100.0
Alive	9	64.5	90.0	3	37.5	37.5	0	0.0	0.0
<i>10-Year results</i>									
Total treated	8	100.0					1	100.0	
Operative deaths	1	12.5					0	0.0	
Lost	1	12.5					0	0.0	
Dead, unrelated causes	0	0.0					0	0.0	
Net followed 10 yrs.	6	75.0	100.0				1	100.0	100.0
Dead of disease	1	12.5	16.6				1	100.0	100.0
Alive	5	62.5	83.4				0	0.0	0.0
<i>Adenocarcinoma (32)</i>									
<i>5-Year results</i>									
Total treated	7	100.0		15	100.0		10	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	1	14.2		1	6.7		1	10.0	
Dead, unrelated causes	1	14.2		0	0.0		2	20.0	
Net followed 5 yrs.	5	77.6	100.0	14	93.3	100.0	7	70.0	100.0
Dead of disease	1	14.2	20.0	3	20.1	21.4	4	40.0	57.1
Alive	4	63.4	80.0	11	73.2	78.6	3	30.0	42.9
<i>7-Year results</i>									
Total treated	5	100.0		12	100.0		7	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	1	20.0		2	16.7		1	14.3	
Dead, unrelated causes	1	20.0		0	0.0		1	14.3	
Net followed 7 yrs.	3	60.0	100.0	10	83.3	100.0	5	71.4	100.0
Dead of disease	0	0.0	0.0	6	50.0	60.0	4	57.1	80.0
Alive	3	60.0	100.0	4	33.3	40.0	1	14.3	20.0
<i>10-Year results</i>									
Total treated	3	100.0		7	100.0		3	100.0	
Operative deaths	0	0.0		0	0.0		0	0.0	
Lost	1	33.3		1	14.3		0	0.0	
Dead, unrelated causes	1	33.3		0	0.0		1	33.4	
Net followed 10 yrs.	1	33.4	100.0	6	85.7	100.0	2	66.6	100.0
Dead of disease	0	0.0	0.0	4	57.1	66.6	2	66.6	100.0
Alive	1	33.4	100.0	2	28.6	33.4	0	0.0	0.0

TABLE 14
LOCAL RECURRENCE

	No.	% Total	% Net
Total cases treated	203	100.0	
Operative deaths	4	2.0	
Lost	22	10.8	
Dead, unrelated causes	15	7.4	
Net cases followed 5 yrs.	162	79.8	100.0
Cases with local recurrence	30	14.2	18.5

bony structure. The opposite breast, supraclavicular nodes, and adjacent tissues beyond the field of dissection are considered as "remote" and are not included in this study of local recurrence.

Local recurrence (Table 14) in the 203 patients equals 14.2 per cent, and this, corrected by eliminating cases not followed five years, rises to an incidence of 18.5 per cent, indicating that roughly one of every five cases exhibited local recurrence.

Time of Recurrence. The time of appearance of the local recurrence has been obtained, and, calculating from the time of initial surgery, is, by postoperative year, as shown in Table 15.

It is to be noted that the figures for each year include the recurrences of previous years. The fact that 7.7 per cent of the local recurrences occurred after five years is somewhat misleading, since it represents but two cases of the total of 203. Since 93.3 per cent of the recurrences were detected within five years, the prognosis as regards appearance of local recurrence after five years is very good.

Some of the patients with local recurrence were treated only five years ago, so that

TABLE 15
TIME OF RECURRENCE

Cases		
	No.	%
Total	30	100.0
Recurrence in less than:		
1 Yr.	9	30.0
2 Yrs.	16	53.3
3 Yrs.	20	66.6
4 Yrs.	27	90.0
5 Yrs.	28	93.3
10 Yrs.	29	96.7
14 Yrs.	30	100.0

Table 16 is complete for all cases for the first five years only.

Twelve of the thirty patients with local recurrence had received postoperative roentgen-ray therapy instituted immediately after initial surgery. All recurrences in this group appeared in a maximum of three years, with average time of recurrence one and one-third years. Nine of the twelve were in group III.

Of the eighteen patients with recurrences who did not receive immediate postoperative roentgen-ray therapy, eight were of group III, and (eliminating the recurrence thirteen years after operation) the average time of recurrence was one and forty-eight hundredths years.

TABLE 16
SURVIVAL OF CASES WITH LOCAL
RECURRENCE
From Date of Operation

Cases			Survived		
Total	Lost	Net followed 5 yrs.	Yrs.	No.	%
30	3	27	1	24	88.8
			2	20	74.0
			3	15	55.5
			5	11	40.6
			7	5	18.5
			9	4	14.7
			10	2	7.4
			14	1	3.7

Comparing the group-III cases that did receive immediate postoperative roentgen-ray therapy with those that did not, no significant difference is found in the time of recurrence or in the survival time.

The recurrences were treated by excision, radon seeds, radiation, and a combination of the three, and no conclusion can be drawn as to respective worth of the forms of treatment.

The recurrence rate (Table 17) is in direct relation to the extent of the disease, that is, the degree of local involvement by the tumor and the extent of lymphatic involvement. This is quite in accord with results of Hoopes and McGraw who, in a study of 246 cases of carcinoma of the breast, found 6.1 per cent recurrence in the ab-

TABLE 17
LOCAL RECURRENCE BY GROUP
Portmann Classification*

Group	Net no	Local recurr.	% Net no	% Total no recurr.
I	48	3	6.2	10.0
II	56	11	19.6	36.7
III	56	15	26.7	50.0
IV	2	1	50.0	3.3
TOTAL	162	30	18.5	100.0

* Based on net number followed minimum of 5 years

sence of axillary metastases and 20.8 per cent in the presence of axillary involvement.

Modified Radical Mastectomy and Recurrence. In some of the patients where advanced age, severe cardiovascular disease, or other illnesses have indicated the least traumatic and briefest possible operative procedure, the pectoral muscles were not removed, but axillary dissection was done. The incidence of local recurrence in this group is contrasted with the incidence of local recurrence in the larger group treated by classical radical mastectomy with removal of the pectoral muscles and axillary dissection. (Table 18.)

Although the group in which the muscles were not removed is too small to permit complete statistical acceptance, the incidence of recurrence is similar to that found in the group in which the muscles were removed.

One of the interesting revelations from the records studied is that of a patient afflicted with a group-I carcinoma of the breast who was treated surgically. At initial operation, the breast was removed, the insertion of the pectoralis muscle divided, the axillary dissection completed, and then the continuity of the pectoralis muscle re-established. Thirteen years later, a recurrence was found and removed from the line of previous section of the pectoralis muscle and the muscles removed. The patient has been followed one year since the last operation and shows no evidence of other recurrence.

Despite the equivalent rate of local recurrence in the two groups, the survival rates reveal that, with the exception of the

group-I cases, there is a slightly higher percentage survival over five, seven, and ten years in those cases treated by classical radical mastectomy. Had all of the cases treated without removal of pectoral muscles been subjected to classical radical mastectomy, the over-all survival rate might have been improved, although the operative mortality might have increased.

Fundamentally, every recurrence is due to failure to extirpate surgically or to destroy by roentgen-ray therapy all neoplastic cells. Implantation of malignant cells into innocent zones at the time of surgery occurs, and probably is the mechanism by which very early recurrences are produced.

The direct, marked relation of the degree of lymphatic involvement to the incidence of local recurrence (Table 18) strongly suggests that, for the most part, the retained tumor cells must exist in lymphatics of tissue unremoved at time of radical mastectomy. These lymphatics may be of the unexcised skin, of the chest wall, of the internal mammary or supraclavicular nodes, or of an inadequately dissected axilla, or of more remote zones.

The normal route of lymphatic flow is from the capillary lymphatics of the skin to the subareolar plexus, into the circumareolar plexus, through the superficial fascial plexus overlying the pectoral muscles, and thence via lymphatic vessels to the ipsilateral nodes, or secondarily to the supraclavicular nodes, internal mammary nodes, and to the contralateral axillary nodes. Obstruction to this normal route of flow does occur with blockage of cortical sinuses of lymph nodes, and may result in retrograde lymphatic drainage with permeation of lymphatics by neoplasm or lymph

TABLE 18
LOCAL RECURRENCE BY TYPE
OPERATION*

Operation	Net no	Local recurrence	
		No.	% Net
Muscles removed	136	25	18.3
Muscles not removed	26	5	19.3
TOTAL	162	30	—

* Based on net number followed minimum of 5 years

phatic emboli.⁸ This phenomenon was noted by Gilchrist and David in their study of carcinoma of the rectum.

The relation of lymphatic involvement to local recurrence is most adequately explained by the mechanism of retrograde lymphatic flow with extension of neoplastic cells, or seeding of malignant emboli from an obstructed lymph node to a more distal structure.

CONCLUSION

An adequate basis for the comparison of the results of different forms of therapy, and therapy by different groups, is urgently needed and should be universally adopted. Among the variables used in classifying the disease should be included an adequate sampling of all lymph nodes, as well as factors from the physical examination as to location, measured size of the lesion, cutaneous involvement, fixation, type of neoplasm present, and the age of the patient.

Some mode of evaluating the degree of involvement of the internal mammary nodes is urgently needed, and a safe method of extirpating the internal mammary nodes should be developed and made a part of radical mastectomy.

SUMMARY

1. In the series of 203 cases presented, the over-all five-year-minimum survival equals 47.7 per cent; the minimum seven-year survival equals 32.9 per cent; the minimum ten-year survival equals 26.7 per cent.

2. The extent of the disease is a more important prognostic factor than the pathological type present.

3. Local recurrence appears to be principally related to the degree of lymph-node involvement.

4. Individual group survivals may be satisfactorily determined under the Pottmann classification.

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SURGICAL TREATMENT OF CANCER OF THE LOWER BOWEL

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FOLLOWING the ingenious procedure performed by Reybard in 1833, nearly all attempts at surgical eradication of cancer of the distal intestine, excluding those located on the last centimeters of the rectum, were made with preservation of the sphincter musculature. However, Miles,²¹ in 1908, presented his method of abdominoperineal excision for all cases and, by virtue of the results achieved, it became the accepted approach for all neoplasms involving the anal canal, rectum, and pelvic colon. During the past decade, the trend has been toward re-establishment of bowel continuity with preservation of the anal-sphincter musculature if the tumor is situated at a safe level above the anal margin. That such recourse is sound is evidenced by the exhaustive studies on the metastatic spread of rectal cancer and by the increasing number of reports.

Radicality does not imply mutilation of unnecessary tissue but rather extensive removal of the proper lymph-bearing areas. It has long been recognized that the lymphatic drainage of the rectum varies according to the site of the injection of a dye, as demonstrated by Cunéo,³ Gerota, Poirier, Cunéo and Delamere,⁵ Villemin, Huard and Montagné, Oliveira, and others. The same is true for the metastatic spread of cancer of the rectum. Many surgeons, both past and present, have reported better results with partial resection than with more extensive excisions.

The term "excision" denotes extirpation of the rectum, anal canal, and perianal skin as performed for low-lying lesions, whereas resection is employed to connote

TABLE 1
DIFFERENCE IN PROGNOSIS BETWEEN
RESECTION AND EXCISION

Author	Resection	Excision
Hochenegg	37.0%	31.0%
d'Allaines, Le Roy, and Dubost	70.0%	40.0%
Eichhoff	42.0%	36.0%
Finsterer (1939)	33.3%	22.5%
Finsterer (1941)	40.4%	30.0%
Schönbauer and Pfab	30.0%	22.0%
Dixon	67.7%	47.7%

removal of ampullary tumors of the rectum. The results are shown in Table 1.

Eiselsberg, Sauerbruch, Pribram, Küttner, Kirschner, Mandl,²⁰ and Aage Nielsen have recorded similar percentages. That this is not mere coincidence but a variation depending upon different spreads of the same lesion located at different levels is well shown by Gilchrist and David who found a five-year-survival rate of 51.8 per cent if the cancer was located below the peritoneal reflection and 65.4 per cent if above. Similar results are reported by Waugh and Kirklin (Table 2), and by Sunderland (Table 3).

The incidence of local recurrence may be regarded as an accurate index of failure of a given operative procedure, but again the precise location of the cancerous lesion is important. Gilchrist and David, for example, cited a local recurrence rate of 18.1 per cent if the lesion was situated above the

TABLE 2
SURVIVAL RATES OF PATIENTS HAVING
GRADE II ADENOCARCINOMA TREATED
BY COMBINED ABDOMINOPERINEAL
RESECTION

Level of lower edge of lesion above anal canal	% Traced patients with nodal involvement alive 5 or more years after operation
0 to 2 cm.	27.8
3 to 6 cm.	23.8
7 to 10 cm.	31.0
11 or more cm.	43.5

Philadelphia, Pennsylvania.

Read before the American Cancer Society, New York, October 30, 1919.

Received for publication, January 3, 1950.

TABLE 3
SURVIVAL ACCORDING TO
ANATOMICAL SITE

Distance above anal margin	Total no	Living and well 5 years	
		Na	%
6 cm. or less	47	22	46.8
6 to 12 cm	36	29	80.6
13 cm. or more	17	13	76.5

peritoneal reflection and 43.5 per cent if below.

Additional reports according to the level of the lesion are available (Table 4).

Obviously, the more the lesion approximates the distal rectum, the poorer is the prognosis. It is recognized that when a dye is injected high in the rectum, the drainage occurs only through the lymphatics of the mesorectum, but if the dye is injected below Kohlihausch's plica or the middle valve of Houston, the drainage occurs through all three areas of spread, as demonstrated by Gerota, Villemin, Huard and Montagné, and Oliveira. That the same is the common feature in the metastatic spread of cancer has been demonstrated by Collei, Kay, and MacIntyre as shown in Table 5.

It is interesting to observe the absence of nodal involvement in the lateral area of spread if the lesion is located more than 3 cm. above the pectinate or anorectal line and that the lateral spread should be responsible for the higher recurrence rate of low-lying lesions. But the two other modes of spread should be analyzed.

Local extension certainly is an important factor in local recurrence but, contrary to the opinion of Gilchrist and David, it does

TABLE 4
LOCAL RECURRENCE AND THE LEVEL
OF THE LESION

Level	% Recurrence
<i>Oppolzer and Nitsche</i>	
1 to 5 cm	62.0
5 to 10 cm.	32.8
10 to 15 cm	31.6
15 to 20 cm	14.2
<i>Wangensteen and Toon</i>	
0 to 5 cm	30.0
6 to 8 cm	25.0
9 to 13 cm	6.3
14 to 20 cm	0.0

not account for the difference in prognosis between high and low lesions. The low rectum is protected by the perirectal fascia, while at a higher level, the rectum and the sigmoid colon do not possess this protective barrier. Furthermore, in a high percentage of cases, the fixation to other structures is of an inflammatory nature, as emphasized by Miles²² and Westhues. Another signifi-

TABLE 5
PERCENTAGE OF INVOLVEMENT OF THE
LATERAL AND THE SUPERIOR AREAS OF
SPREAD ACCORDING TO THE LOCATION
OF THE LESION IN CASES WITH NODAL
INVOLVEMENT

Location	% Lat. area	% Sup. area
Anus and last 3 cm. of rectum	54.5	100
High rectum	No cases	100
Rectosigmoid	No cases	100
Above rectosigmoid	No cases	100

cant observation was cited by Dukes,⁵ who found, after studying 1000 surgical specimens, that the prognosis of cancer of the rectum is not related to the location of the tumor unless there is node involvement. In such instances, the lower lesions offer a poorer prognosis. Venous involvement has

TABLE 6
SURVIVAL ACCORDING TO
ANATOMICAL SITE²¹

Distance above anal margin	No invasion			Invasion		
	Total no	Living and well 5 years		Total no	Living and well 5 years	
		No	%		Na	%
6 cm. or less	27	16	59.3	20	6	30.0
6 to 12 cm	28	23	82.1	8	6	75.0
13 cm. +	16	13	81.3	1	0	0.0

been reported to be greater in higher lesions, but a recent and reliable study made by Sunderland proved the contrary to be true. His results are of paramount importance for appreciation of the role of the venous invasion in prognosis according to the level of the lesion (Table 6).

As stressed by Lahey, blood invasion carries with it a very cloudy prognosis but, as pointed out by Seefeld and Baugen and by Dukes,⁷ this has little significance for

local spread but only for the distant metastases.

The conclusions we can draw from Table 6 are decisive. 1. The prognosis even without vein invasion is poorer in low lesions. 2. There is still a marked difference according to the level of the lesion in spite of vein invasion. Should vein invasion play a major role in the prognosis, all cases with involvement of the blood vessels would have about the same prognosis. This is sufficient evidence that other factors should be invoked. 3. The distant metastases to the lung would be more frequent if the addition of the vessels of the middle and inferior hemorrhoidal could play a role in the metastasizing of the growth. 4. As we have shown previously, the important cause of the poor prognosis is local recurrence. It is generally agreed that vein involvement is of very little, if any, concern, as far as local recurrence is concerned. From this point, venous involvement cannot explain the higher incidence of local recurrence.

That the lymphatic embolism is the most important mode of spread in carcinoma has long been recognized, but to what extent can it influence the prognosis according to the level of the lesion? The answer is well illustrated in the work of Villemain, Huard and Montagné. It becomes evident that the upward spread is of no concern, and only the downward or the lateral spread can play a role in the difference in prognosis. Metastasis to the inguinal glands does occur but only in a small percentage of cases where the lesion does not involve the anal canal.

Why is it necessary to show the importance of the lateral spread if most surgeons and pathologists pay little heed to it? There are two important reasons: 1. The glands of the lateral zone of spread are imbedded in the fat tissue of the lateral ligaments and of the lateral pelvic wall in such a manner that they are not visible to the surgeon. Further, few surgeons, searching for involved nodes, palpate the lateral ligaments. The only reference we found was that recorded by d'Allaines, Le Roy, and Dubost,

who encountered several instances of thickening of these structures. 2. The Spalteholz method has become the accepted procedure for pathological examination of surgical specimens. By this technique, a contrast medium is injected into the superior hemorrhoidal vessels, and the contiguous glands are searched for metastases. The lateral ligaments on an anterolateral position are overlooked. Another reason for failure to discover involved nodes in the lateral ligaments is that the surgeon does not carry his lateral resection widely enough to obtain sufficient material for examination by the pathologist.

Another source of error, in our opinion, is a misinterpretation of the "lateral spread." According to Miles,²² the lateral zone of spread lies between the levators and the pelvic fascia. His studies were based on the work of Poirier, Cunéo, and Delamere,⁵ who confirmed the studies made by Cunéo and Marcille⁴ that the lymphatics following the middle hemorrhoidal vessels are constant. The investigations of the anorectal area demonstrate that these lymphatics follow closely the middle hemorrhoidal vessels and that these vessels are located in the lateral ligaments. This is clearly evidenced where the lateral ligaments are visualized with the contained lymphatics well above the levator muscles. To demonstrate this fact, we have a series of cases in which a dye was injected prior to the operation and its spread through the lateral ligaments was observed to be a constant feature. Only in a few instances were thin lymphatics visualized between the levators and the pelvic fascia, but never was a node found in this location. This is important because it emphasizes not only the significance of the lateral spread but also that the important structures to be widely resected are the lateral ligaments rather than the levator muscles. This fact is well substantiated in the pathological studies made by Wood and Wilkie and by Dukes⁷ who showed that the levators are not a place where metastasis occurs but rather are subject to direct spread. But even a wide re-

section of the lateral ligaments may not prove to be the last word for resection of the lateral gland-bearing area. A wide pelvic lymphadenectomy should be a part of the surgical treatment of cancer of the lower rectum and should include resection of the iliac nodes.

It is not our belief that the lateral ligaments are the only structures contributing to the lateral mode of spread. The sacral glands, both lateral and middle, require wide excision, together with the sacral fascia.

Our experience is based on a personal series of 1022 patients with cancer in the colon and rectum, of which number the lesions in 1001 were located in the sigmoid, the rectum, or the anal canal. This group is sufficiently large that the conclusions drawn are not a mere presumption or hypothesis but rather are to be evaluated on a factual basis. On the premise of the investigations previously cited, the surgical approach in our clinic has been as follows.

APPROACH

1. All cancerous lesions involving the anal canal and the last 3 cm. of the rectum are removed only by the Miles abdominoperineal method of excision. Because of the variation in the survival rate and of the frequency of local recurrence according to the location, we are convinced that even this operation is now not sufficiently radical for low lesions, and for these reasons, pelvic lymphadenectomy is recommended. This procedure has been performed in a small number of cases.

2. When the lesion is located above this 6-cm. level, the entire rectum, lateral ligaments, and levators as well as the mesorectum and mesosigmoid are removed by the procedure we term "proctosigmoidectomy," in which high ligation of the inferior mesenteric vessels is made, and the sphincter musculature is preserved.

3. Lesions in the sigmoid are resected with immediate establishment of continuity. The Mikulicz-Rankin and the Hart-

mann operations have now few indications. Excluding those for the right, the transverse, and the descending colon, 795 radical extirpations were performed with a mortality rate of 5.0 per cent.

TABLE 7
TYPE OF RADICAL PROCEDURES
Authors' Series

Type	No. cases	Deaths	Mortality %
1. Sigmoidectomy	112	9	7.8
2. Abdominoperineal excision	184	7	3.8
3. Abdominoperineal proctosigmoidectomy without colostomy and with preservation of anal sphincters	486	23	4.9
4. Hemicolectomy and proctosigmoidectomy with preservation of the sphincters	10	1	10.
5. Perineal excision	3	0	0.
TOTALS	795	40	5.0

The resectability rate has been found to be 89 per cent. It is known that 58.4 per cent of those patients upon whom a modified Hochenegg procedure was performed, which we term "abdominoperineal proctosigmoidectomy" without colostomy and with preservation of the anal sphincter muscle, are alive and well five years following operation. This incidence of five-year salvage includes unfavorable cases—those with glandular involvement and/or local extension—and favorable cases—those without nodal involvement or local extension—but excludes those with liver metastases. The local recurrence rate, computed in late 1948, was 17.9 per cent, and sexual impotence in the male, 8.3 per cent.

Postoperative Course. Ordinarily patients are permitted out of bed the second or third postoperative day and are usually discharged from the hospital on the tenth postoperative day. Complete healing of perineal wound occurs in three weeks and patients are able to return to work one to two and one-half months following operation.

SUMMARY AND CONCLUSIONS

On observing the techniques for excision or resection of cancer of the rectum, one

relevant fact becomes surprisingly manifest. The extirpation of the lateral and downward areas of spread is too meager.

The excision of the skin around the anus is too small and permits spread to the inguinal nodes, but the rarity of local recurrence when the tumor does not involve the anal and perianal structures is decisive evidence that this mode of spread is of little importance.

As almost all local recurrences are in the pelvis, the other two modes of spread should be regarded as the pathway for metastases. It is universally recognized that the upward spread is by far the most important mode of spread, and some authors even believe that it is the only significant one. But how can we explain the difference in prognosis between low and high lesions?

It is a well-known fact that when a dye is injected in the rectum above the middle valve of Houston, all the dye follows the upward direction along the superior hemorrhoidal vessels, but when injected below this valve, it follows not only the mentioned pathway but also the lateral spread. These investigations made on cadavers were verified by us *in vivo*. The possibility that metastases may travel the same pathway is suggested by several things: 1. Several authors have reported that carcinoma of the lower rectum has a much poorer prognosis than have higher lesions. 2. Local recurrence is directly proportional to the site of the tumor. The lower the tumor in the rectum, the higher the percentage of local recurrence. 3. In the few reports mentioning the lateral spread, gland involvement in this area was found to be high when the lesion was in the low rectum, whereas it very seldom occurred in high lesions. 4. Large excision of the levator muscles has been overemphasized, while the lateral ligaments and the other structures of the pelvis along

the external, internal, and common iliac vessels containing the nodes where the lymph of the rectum is carried out through the lymphatics running along the middle hemorrhoidal vessels, are left *in situ*. The small amount of the lateral ligaments resected, as seen in the surgical specimens after resections or excisions, is strong evidence of the lack of radicality of the present procedures for the eradication of one of the areas of spread of cancer of the rectum. 5. Several causes can be mentioned for overlooking the nodes in the lateral areas, but the more important are: (1) the concept of lateral spread as described by Miles was universally adopted. In spite of the proposition of some authors that a revision on the subject is necessary, nothing has been done in this respect. In consulting the anatomical studies on the subject, however, it is clear that the lateral spread cannot be resected sufficiently by removing only the levators. The lateral ligaments are the bridge over which very important lymphatics of the lateral areas have to pass. The 1 or 2 cm. of these structures removed by the usual techniques, in contrast with the entire removal of the mesorectum, show well how economical these excisions are. (2) How can a pathologist report metastasis in the lateral area of spread if the surgeon sends only an operative specimen with such a small amount of the lateral lymph-node-bearing area?

As a conclusion to our point of view, we suggest a pelvic lymphadenectomy as a complement to the abdominoperineal excision proposed by Miles. Extirpation of the Denonvilliers fascia should prove of value also, as suggested by Reinhold.

Local and venous spread have been mentioned to show that they cannot be invoked as the cause of the different prognosis of low-lying lesions.

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RADIOACTIVE PHOSPHORUS

I. In the Treatment of Lymphatic Leukemia

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THIS paper is the first of a proposed series of communications reporting a nine-year experience with P^{32} in the treatment of lymphomas, leukemias, and allied disorders.

For many years, external whole-body and local irradiation with roentgen rays have constituted established conventional methods for the treatment of lymphomas and leukemias. In the United States, Senn, in 1903, first used roentgen rays therapeutically in the lymphomatous diseases. Thereafter, roentgen rays were employed with increasing frequency in the treatment of the lymphomas and leukemias. In 1924, Minot and his co-workers^{6, 7} published an important early summary revealing that definite palliation of chronic leukemia, both myeloid and lymphoid, could be achieved with this agent, without resulting, however, in significant increase in actual survival time. In recent years, it has been possible to accomplish whole-body irradiation from within the body by means of radioactive isotopes. Cure of the leukemias by any form of external-radiation treatment has never been effected nor is it suggested

that radioactive isotopes, principally radioactive phosphorus (P^{32}), are curative.

This paper deals with our experience at Memorial Hospital in the palliative treatment of lymphatic leukemia with P^{32} . The period covered dates from April 20, 1940, when we employed P^{32} for the first time to the arbitrary termination date on May 5, 1949; i.e., the initial dose of the first course was given to the first patient on April 20, 1940; the first dose of the last course to the last patient on April 29, 1949, and the last dose of this course on May 5, 1949. Investigations with P^{32} are being continued in our clinic, and our experience is accruing still further.

DOSAGE AND TECHNIQUE OF PREPARATION OF P^{32}

The P^{32} used in the early part of this work was obtained as a 1.5 to 3.0 per cent solution of disodium hydrogen phosphate, with an activity of 0.2 to 0.5 mc. per cc. In the latter part of 1946, P^{32} produced in the nuclear reactor at the Oak Ridge National Laboratory became available for civilian use, and this material has been used at Memorial Hospital since that time. The chemical state of this P^{32} varied from time to time, but it was usually supplied as a solution of disodium hydrogen phosphate or of phosphoric acid, with an activity of 1 to 3 mc. per cc. The specific activity of the pile-produced isotope was rather high, being of the order of 1 mc. P^{32} per 0.05 mg. P^{31} , whereas that of the isotope made in the cyclotron was only about 1 mc. P^{32} per 60 mg. P^{31} . Even the amount of P^{31} present in the material produced in the cyclotron is not likely to be of physiological significance at the dosage level employed, since the nor-

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The authors are indebted to Dr. John S. LaDue and Dr. John Leach, both of the Department of Medicine of the Memorial Center for Cancer and Allied Diseases, for their co-operation in carrying out this study.

The P^{32} used in the early part of this work was prepared in the cyclotron of the Radiation Laboratory of the University of California at Berkeley, or in the cyclotron of the Radioactivity Center of the Massachusetts Institute of Technology, through the courtesy of Dr. John H. Lawrence and Dr. Robley D. Evans, respectively. Since the latter part of 1946, P^{32} produced in the nuclear reactor at the Oak Ridge National Laboratory has been used.

Autopsy-tissue-analysis studies, reported in Table 3, are the work of Dr. John M. Kenney, Santa Rosa, California.

Received for publication, April 20, 1950.

mal human dietary intake of phosphorus is 1 to 2 gm. per day. The preparations obtained from Oak Ridge contained chlorides and other inorganic substances in amounts too small to cause physiological changes.

When the solution containing P^{32} was received, it was diluted, if necessary, with distilled water to a concentration of approximately 1 mc. per cc.; 0.2 cc. of this stock solution was then withdrawn for physical measurements. From this, a series of dilutions was prepared containing approximately 0.05 to 5.0 mc. per cc. Samples of the diluted material (0.5 or 1.0 cc.) were then placed in shallow, flat-bottomed metal dishes, dried at 110° C. and measured against a uranium standard of the same geometry as the unknown. After the measurements were completed, a decay table was prepared showing the number of cubic centimeters of the stock solution that contained 1 mc., on each day for the next two weeks. The stock solution was kept in a glass bottle in the laboratory refrigerator. This was done not only to prevent the growth of mold in any solutions that were not strongly acid, but also because the metal walls of the refrigerator afforded complete protection of personnel from the small amount of radiation that penetrated the glass bottle.

It was recognized that some of the P^{32} administered orally always escapes absorption in the gastrointestinal tract and is lost in the feces. Early measurements indicated that this loss amounted to only about 20 to 25 per cent, and even smaller losses could be expected with material of the high specific activity that was available later. It has been noted also that intravenous administration, at least in 4- to 5-mc. doses, has been followed by appreciable loss of P^{32} in the urine in the first day. The intravenous use of P^{32} , moreover, involves processing the material to remove pyrogens, with a slight loss by radioactive decay during the time required for the procedure. There is, in addition, a small but appreciable exposure of the laboratory and medical personnel during processing and injection,

as well as considerable expense for their time. Hence, it was felt that the advantages of intravenous administration were outweighed by the disadvantages, and it was employed only twice in the entire work. With the technique used, the operator received less than 30 mr (milliroentgens) to the wrists and whole body during one month in which 100 mc. was handled.

CASE MATERIAL

In this survey, eighty-four patients received P^{32} . However, since thirteen patients either had inadequate follow-up or were lost to follow-up, only seventy-one patients were considered in the true study group. The majority of these patients was obtained from the Lymphoma Clinic and Medical In-Patient Service of Memorial Hospital, and a small number came from the private practice of one of the authors (L.F.C.)

Early in the work, no attempt at case selection was made. As the study progressed, however, it was appreciated that there were definite limitations to the exclusive use of this therapy in patients with bulky nodal disease and considerable splenohepatomegaly. When, less commonly, a patient was seen who presented chiefly the hematological manifestations of the disease without bulky lymphadenopathy and splenohepatomegaly, or who displayed them minimally, P^{32} alone was the treatment of choice. No patients, irrespective of the extent of disease in lymph nodes, spleen, or liver, were denied P^{32} if the bone marrow was neither severely hypoplastic nor bordering on aplastic, and so long as a marked peripheral subleukemic (leukopenic) blood picture did not exist.

The entire survey group of seventy-one patients was subdivided further into acute and chronic cases. Such classification was dependent principally on the clinical and hematological status of the individual patient rather than on the extent of temporal survival. Using these criteria, fifty-three patients were classed as chronic and eighteen as acute.

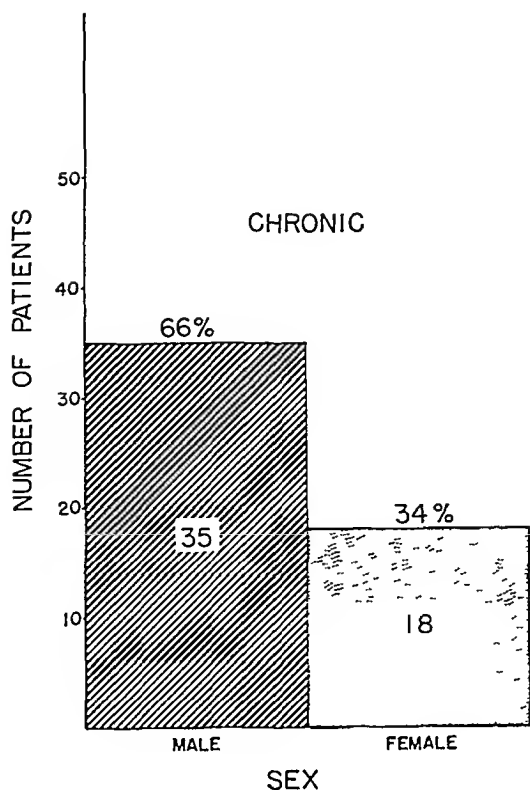


FIG. 1. The sex incidence in a series of fifty-three patients with chronic lymphatic leukemia treated with P^{32} .

Chronic Cases. Only ten patients were treated solely with P^{32} . As the need for additional methods of treatment arose, means supplementary to P^{32} were employed in the other forty-three chronic patients. Other methods used were local roentgen-ray radiation, Heublein (total body) radiation, potassium arsenite (Fowler's solution), ethyl carbamate (urethane), folic acid antagonists, nitrogen mustard and nitrogen-mustard congeners, and in one instance, the radium-element pack.

Acute Cases. Nine (50 per cent) of the eighteen patients classified as acute were treated only with P^{32} , and in every case with a dosage of P^{32} well below the therapeutic level (0.1 mc. per Kg. body weight) used in chronic lymphatic-leukemia patients, either because of the precarious condition of the patient, or for fear of inducing a hemorrhagic catastrophe. The

remaining nine patients received cautious local roentgen-ray radiation in addition to P^{32} .

Pertinent Histories. One patient gave a definite history of leukemia in two paternal uncles. In this same family, one first cousin also had Hodgkin's disease, and both parents of the patient had died of cancer. In another instance, one of twin children had acute leukemia and the other did not. Although the children were of the same sex, we have not been able to determine whether they were monozygous. It is also of interest that in one child in our series, a Paul-Bunnell heterophile test was positive at a titer of 1:128. Southam, Goldsmith, and Burchenal are preparing a report on the incidence of positive heterophile reactions in leukemic patients.

Sex, Race, and Age. Of the total number of patients, forty-eight (68 per cent)

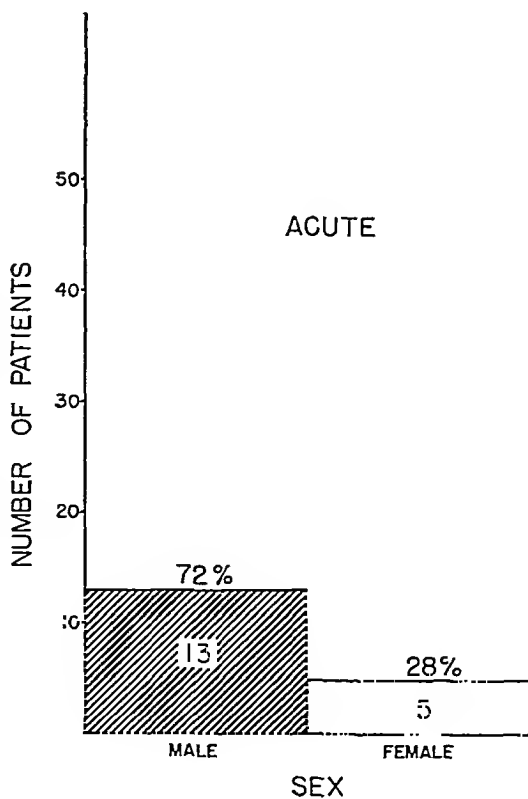


FIG. 2. The sex incidence in a series of eighteen patients with acute lymphatic leukemia treated with P^{32} .

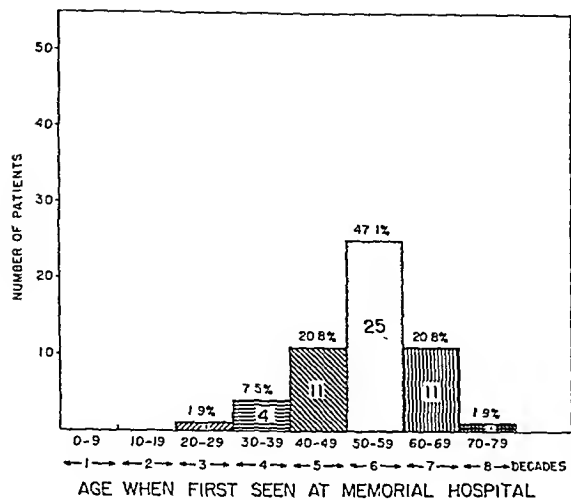


FIG. 3. The age distribution in a series of fifty-three patients with chronic lymphatic leukemia treated with P^{32} . This graphic illustration is based on the age of the patient when seen for the first time at Memorial Hospital.

were men, and twenty-three (32 per cent) were women. In the chronic group, there were thirty-five men (66 per cent) and 18 women (34 per cent); in the acute, 13 men (72 per cent) and 5 women (28 per cent). All these figures approximate closely the sex incidence reported by Minot and Isaacs,⁷ and Lawrence et al.⁵ It is of interest that every patient in the entire group, both chronic and acute, was white. There is a large Negro population in New York City, and Negro patients are numerous in other clinics at Memorial Hospital. Hence, it is difficult to explain the absence of Negroes in this study.

The youngest patient seen was 1.3 years of age, and the oldest was 74. These ages refer to the AGE WHEN THE PATIENT FIRST PRESENTED HIMSELF AT MEMORIAL HOSPITAL, rather than to the age of onset of disease. The average age for the entire group of seventy-one patients was 41.8 years. The average age for the chronic patients was 52.9 years. This figure is almost exactly that reported by Wintrobe and Hasenbush, and recently by Lawrence et al.,⁵ but their statistics are predicated on age of onset. The youngest person in the chronic lymphatic series was 24 years old, the oldest, 74. In

the acute classification, the youngest patient was 1.3 years old, and the oldest, 38. The sex and age incidences are represented graphically in Figs. 1, 2, 3, and 4.

TREATMENT

Almost all of the patients, except those diagnosed and treated in the private office of one of the writers (L.F.C.), were seen first in the diagnostic clinic of Memorial Hospital, where complete history and physical examination, peripheral hemogram, and urinalysis were performed, and chest roentgenograms were made. Early in the work, sternal-marrow aspirations were done without regularity, but by 1946, they became a part of the routine procedure carried out at the time of the initial visit. Further roentgenographic and special chemical determinations were made when they were indicated clinically. A small number of patients were seen initially on direct hospitalization. For the most part, these were patients with acute lymphatic leukemia, and the stated studies were done while the individual was an in-patient. Once the diagnosis was established, the patients were observed, treated, and followed carefully at regular intervals. All clinical and laboratory examinations were well standardized, whether the patient was a clinic out-patient, a hospital in-patient, or an out-

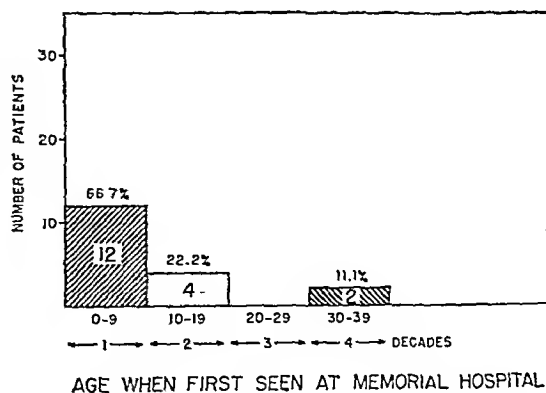


FIG. 4. The age distribution in a group of eighteen patients with acute lymphatic leukemia treated with P^{32} . This graphic illustration is based on the age of the patient when seen for the first time at Memorial Hospital.

patient in the office of one of the authors. All peripheral-blood smears and marrow aspirations were examined by qualified personnel of the hospital's hematology laboratory.

As previously mentioned, no particular selection of cases was attempted, although the group without bulky peripheral lymphadenopathy and enlarged spleen and liver was preferred, since these patients fared better with P^{32} than the group with easily palpable disease. Patients in the chronic group, in whom the only objective evidence of lymphatic leukemia was hematological, simulated the clinical appearance of chronic myeloid leukemia, a disease in which P^{32} exerts satisfactory control. The effects of P^{32} on chronic myeloid leukemia have been reported already,^{1, 2, 3, 4, 8} and will be the subject of a paper to be published shortly by the authors.

All patients received P^{32} orally, except for two instances very early in our clinical trials, when it was given intravenously. In the chronic group, the therapeutic dose of P^{32} approximated closely or was calibrated at 0.1 mc. per Kg. of body weight, dividing the dose into individual daily doses as close to 1.0 mc. as feasible. Thus, a 70-Kg. patient was given 1.0 mc. daily for seven successive days. When the physician decided to treat such a patient, he sent a written or telephoned order to the laboratory stating the name of the patient, the number and size of the daily doses required, and the date of the first dose. The requisite number of vials were then dated, and by the use of the decay table, sufficient P^{32} solution was pipetted into each vial so that it would contain 1 mc. on the date indicated. The dated vials were then packed in a container and given to the patient with instructions to drink the contents of each on the appropriate date. In order to diminish the loss of P^{32} as insoluble phosphate in the feces, the patients were cautioned to eat nothing for four hours before or after taking the P^{32} , and to take no milk, cheese, or iron or bismuth medication during the period of therapy. To re-emphasize these instructions,

a typewritten form enumerating all the oral instructions was enclosed in the package containing the vials of P^{32} . These precautions obviated contamination of the P^{32} with food undergoing digestion and facilitated absorption. Since approximately 20 to 25 per cent of the ingested dose is lost in the feces, keeping the individual doses down to small increments of 1.0 mc. per dose allowed for absorption of approximately 75 to 80 per cent of the total dose.

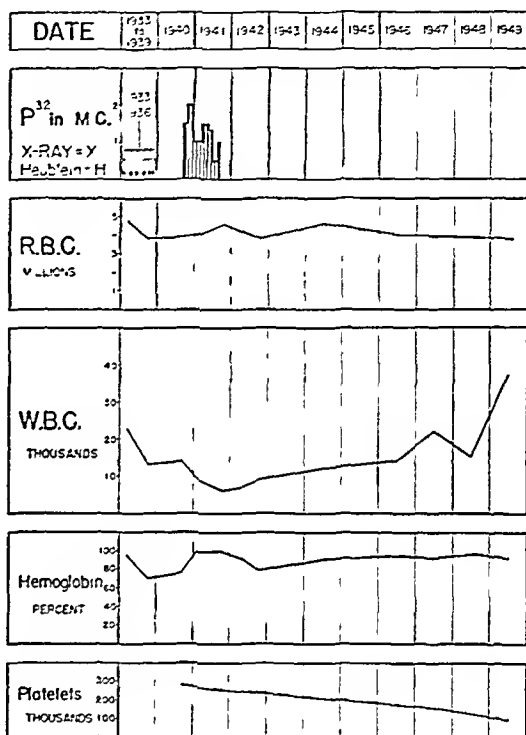


FIG. 5. This chart illustrates a patient with chronic lymphatic leukemia who, after initially receiving local external roentgen-ray radiation on four occasions from 1933 to 1936, as well as two courses of Heublein total-body roentgen-ray radiation consisting of 25 r in 1935 and 25 r in 1936, had no need for further treatment until 1940. From November 25, 1940, to May 28, 1941, a total dose of 12.0 mc. of P^{32} was administered. Both roentgen-ray radiation and beta radiation by P^{32} seem to have given long-term control of the hemogram and clinical state of this patient, who is still living and well, but who is beginning to demonstrate more aggressive disease.

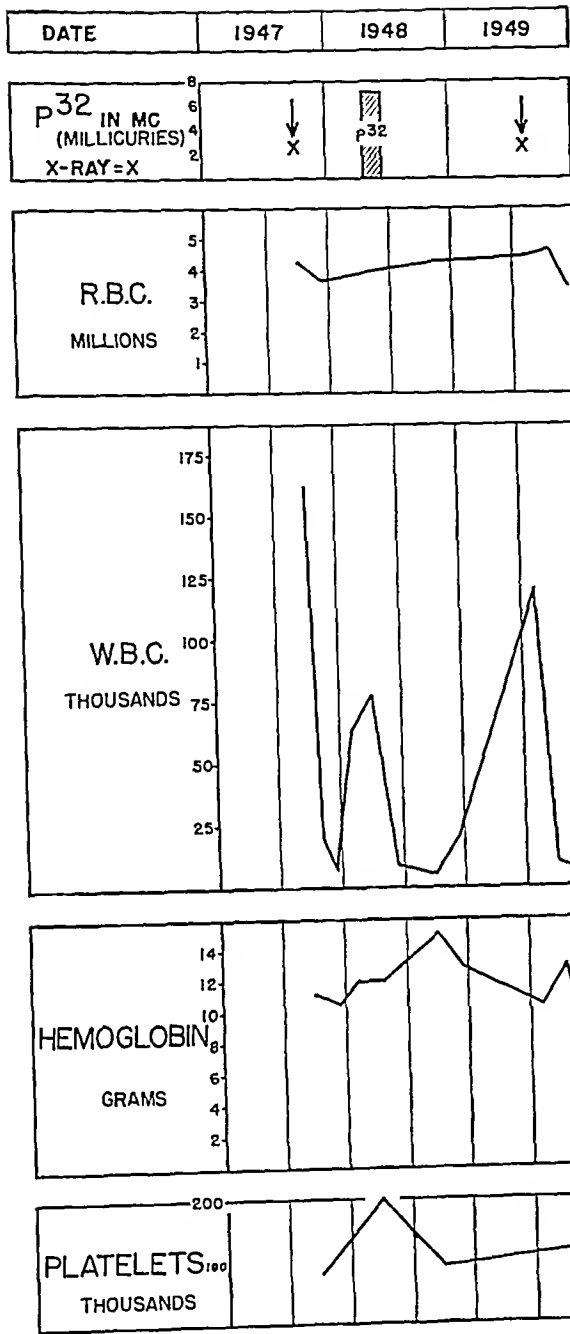


FIG. 6. This figure illustrates how both roentgen rays and P³² may be employed to augment one another in attempting objective control of the levels of red blood cells, hemoglobin, white blood cells, and platelets in chronic lymphatic leukemia. The patient is a 56-year-old man treated first with external roentgen-ray radiation directed to the peripheral node-bearing areas, and then with 7.0 mc. of P³² resulting in a substantial clinical and hematological remission for fifteen months. Upon relapse, roentgen-ray radiation was em-

TABLE 1
DURATION OF LIFE IN CHRONIC LYMPHATIC LEUKEMIA

Author	Patients	Treatment	Average duration yrs.*
Minot, et al. ⁷	30	None	3.33
Minot, et al. ⁷	50	X-rays	3.53
Wintrobe & Hasenbush	23	X-rays	2.33
Reinhard, et al.	14	X-rays & P ³²	2.46
Lawrence, et al. ⁸	97	X-rays & P ³²	4.50
Diamond, Craver, Woodward, & Parks	53	X-rays & P ³² ; P ³² & other agents	4.20

* Average duration in years after onset of first symptoms.

When the disease was influenced beneficially by P³², there were objective changes in the hemogram, as evidenced by a rise in the hemoglobin or red-cell count, a fall in total white cells, and, occasionally, diminution in size of palpable lymph nodes, spleen, and liver. Alteration in size of nodes, spleen, and liver was indeed evanescent. Additional courses of P³² therapy were given when indicated clinically, and when the hemogram and marrow showed return of proliferative activity. The good responses of two patients are illustrated in Figs. 5 and 6. A table summarizing the duration of life in chronic lymphatic leukemia as reported by different authors is shown in Table 1.

TABLE 2
SURVIVAL TIME OF PATIENTS

Group	No.	Survival			
		1st Mem. Hosp. visit		Onset of symptoms	
		Mos.	Yrs.	Mos.	Yrs.
Acute	18	2.9	0.24	4.5	0.38
Chronic	53	2.9	2.4	50.6	4.2

DISCUSSION

In no instance in the acute group could P³² be shown to have any beneficial effect. The survival times for both groups, calculated as survival FROM THE TIME OF THE FIRST MEMORIAL HOSPITAL VISIT and from the time of the onset of the first symptom, are shown in Table 2. All these figures are averages. The survival time in years from

ployed again. The patient is alive and well, though anemic. No blood transfusions were given.

TABLE 3

CHRONIC LYMPHATIC LEUKEMIA
Percentage Incidence of Pertinent Presenting
Symptoms in a Series of Fifty-Three Patients
Treated with P³²

<i>Symptom</i>	<i>No. patients</i>	<i>Per cent</i>
Bleeding phenomena	9	17.0
Fatigue and/or weakness	27	50.9
Weight loss	13	24.5
Enlarged nodes	32	60.4
Pain	15	28.3
Fever	8	15.1
Nausea and/or vomiting	1	1.9
Pruritus	7	13.2
Cough	12	22.6
Anorexia	2	3.8
Rash (skin lesions, urticaria, etc.)	4	7.5
Dyspnea	6	11.3

the time of the first Memorial Hospital visit for the chronic group is lower than for the series reported by Minot and Isaacs⁷ and Wintrobe and Hasenbush, but their calculations were based on the time of onset of symptoms. If, however, one calculates from onset of symptoms in our group, the survival figures are significantly longer than those reported by these writers.

Lawrence reports in his recent communication⁷ that 33 per cent of his group has survived five or more years and 10 per cent, eight or more years. These figures, however, are predicated, admittedly, from onset of disease. It is significant that this series has been larger than ours. Our five-year-survival rates computed FROM THE DATE OF FIRST HOSPITAL VISIT, show six of fifty-three patients alive five or more years, or 11.3 per cent; whereas, computation from onset of first symptoms reveals thirteen five-year survivals, or 24.5 per cent. Our eight-year-survival rate is 1.9 per cent (one patient of fifty-three), from the time of the first hospital visit, and 7.6 per cent, four patients, when reckoned from onset of first symptoms.

Survival times are elevated considerably if calculated from onset of symptoms. It is most difficult to know what the first symptom was and when it occurred, especially since these symptoms may resemble those characteristic of coxial infection. Patients

seen in our clinic presented a variance from a few weeks to as long as sixteen years from the so-called time of onset to the time of the first hospital visit.

Pertinent symptoms and signs in the chronic group are given in Tables 3 and 4.

It is of interest that these patients had numerous associated and intercurrent diseases and complications. These are represented graphically in Fig. 7. One patient in the series of seventy-one was an employee in a plant making paradichlorobenzene. Our longest survivor is the patient described in Fig. 5. He has survived sixteen years from his first hospital visit and eighteen years from onset of symptoms. He has been well up to the present, and, since his course of P³² in 1941, has needed no further therapy. He is now beginning to relapse.

In only two patients of the chronic group (3.8 per cent) was a terminal, acute picture of the disease observed. Two patients (3.8 per cent) experienced radiation illness after P³² was administered, manifested by nausea, vomiting, diarrhea, dizziness, or syncope. Only one patient died with an aplastic anemia attributable to P³².

In 85 per cent of all the patients in the group, P³² caused at least a transitory fall in total peripheral white-cell count. In approximately 50 per cent, the hemoglobin and the red-cell count were not altered significantly in either direction. Adenopathy and splenohepatomegaly were affected inconsistently and often not at all measurably. Reasons for this failure seem obvious

TABLE 4

CHRONIC LYMPHATIC LEUKEMIA

Percentage Incidence of Pertinent Presenting Signs
in a Group of Fifty-Three Patients

<i>Sign</i>	<i>No. patients</i>	<i>Per cent</i>
Pallor	11	20.8
Adenopathy*	48	90.6
Splenomegaly*	38	71.7
Hepatomegaly	27	50.9
Skin lesions	3	5.7

* The high proportion of patients having adenopathy or splenomegaly suggests that the combination of local roentgen-ray radiation and P³² would offer better control than P³² alone, since the latter has little effect on bulky disease.

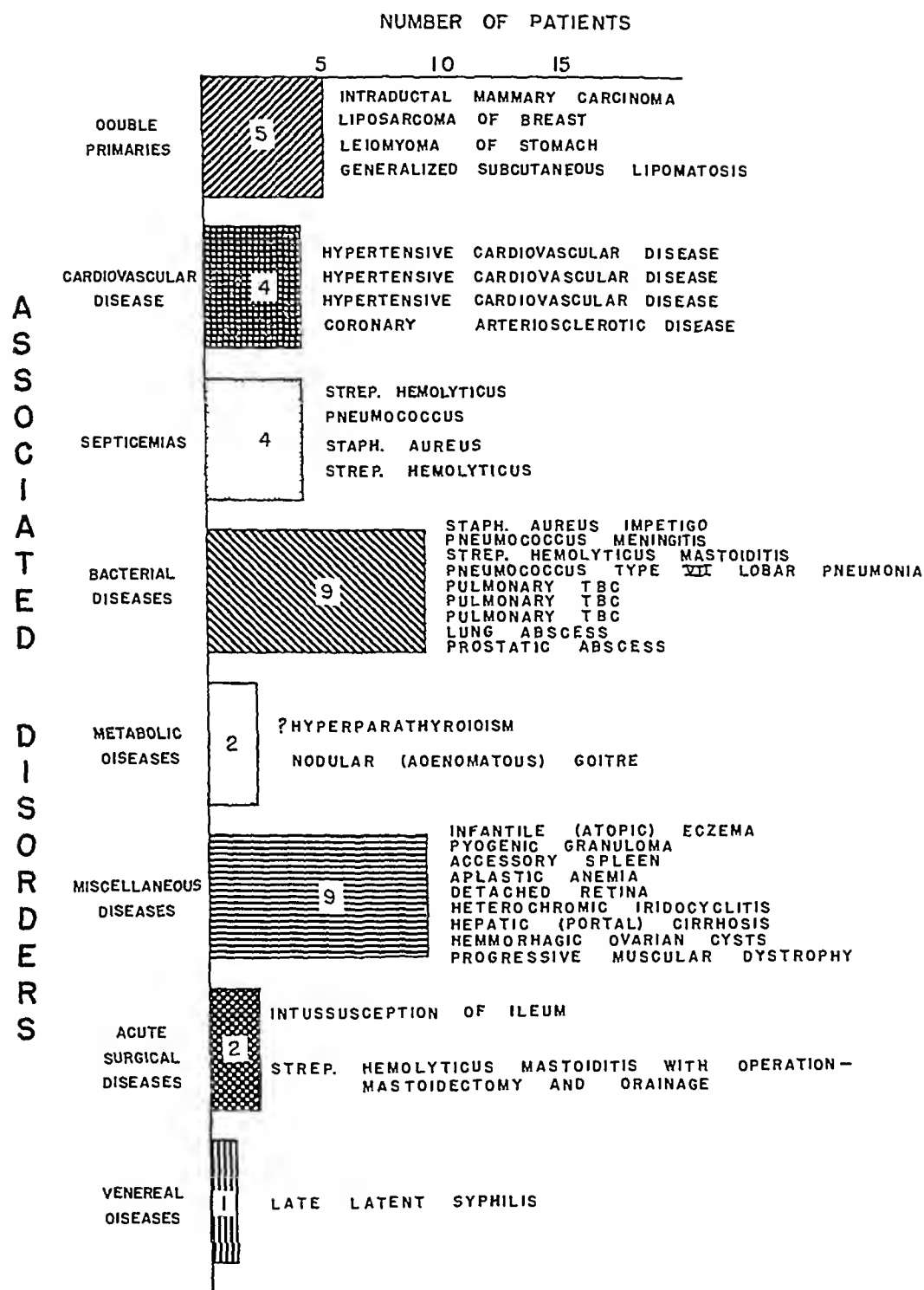


FIG. 7. This graph illustrates the varied associated diseases encountered in the entire group of seventy-one patients with lymphatic leukemia treated with P^{32} . It is of importance to note the incidence of so-called "double-primary" neoplasms, and the significant number of intercurrent septicemias and bacterial infections.

from the known limited beta penetration power of P^{32} (on the average only 2.0 to 3.0 mm. in tissue), as well as from the fact that although preferential uptake by nodes, spleen, and liver may be two to ten times that of the body as a whole, such uptake is insufficient to deliver enough radiation to these structures to cause regression with any regularity. Detailed tracer-uptake studies are given in Table 5.

From these observations, P^{32} may be noted to exert a definite influence in the great majority of cases on the total peripheral white-cell count, but, unfortunately, the hemogram reflects only one sign of lymphatic leukemia. When bulky palpable disease is present, P^{32} should be augmented with judiciously applied local roentgen-ray radiation.

The well-known limiting factors of P^{32} are the relatively unselective uptake of P^{32} by diseased tissue as opposed to normal tissue, and the slow but prolonged rate of irradiation of normal elements of the bone marrow by P^{32} .

CONCLUSIONS

A study of seventy one patients with lymphatic leukemia treated with P^{32} , with roentgen-ray radiation and P^{32} , and with P^{32} and other chemotherapeutic agents, culminating a nine-year experience, has been reviewed. In agreement with Lawrence et al.,⁷ we believe comfortable and useful life has been prolonged. Depending upon whether survival rates are calculated from the first hospital visit or from the onset of first symptoms, these rates in terms of years are lower and higher, respectively, than most other reported series.

The five-year-survival rate when computed from the first hospital visit is reported as 11.3 per cent. When it is computed from the onset of first symptoms, it is 24.5 per cent. It is suggested, from these and other examples of the great hiatus between onset figures and first hospital-visit figures, that it is undesirable to calculate survival rates from the so-called onset of disease. This point is emphasized when one

TABLE 5
ACUTE LYMPHATIC LEUKEMIA
 P^{32} Tracer-Uptake Study Determined by
Autopsy-Tissue Analysis

Tissue	$\mu\text{c./kg.}$ tissue weight
Vertebrae	6 679—7 434
Rib	6 092
Marrow	38 947
Rib (without marrow)	4 786
Muscle	2 552
Testicle	9 861—11 287
Perihepatic node	15 570
Kidney (1 light)*	8 908—11 298
Kidney (2 red-blue)*	11 713—13 532
Lymph node	7 342—18 979
Heart muscle	9 709—15 269
Pancreas	16 089
Lung	11 020
Liver	15 163
Spleen	14,472—14 829

* Different areas of the same kidney

This table is important because it reveals a significant uptake of P^{32} by bone marrow, as compared to other tissues. Pharmacologically, however, P^{32} must be considered a general cell poison. This is in contrast to I^{131} , which, by virtue of its remarkably selective uptake by the thyroid gland, is considered an agent injurious to specific cells.

considers the wide variations noted in the natural history of this disease. One patient in our series reported symptoms compatible with, but not necessarily indicative of, lymphatic leukemia sixteen years prior to presenting himself at our clinic.

We want also to emphasize the fact that our five-year-survival rates and those reported by others are considerably in excess of those for malignant melanoma, and cancer of the esophagus, pancreas, stomach, and lung, and that the undue pessimism concerning lymphatic leukemia reigning in the minds not only of the public, but also of the medical profession, should be dispelled by these figures. No physician is completely capable of predicting the life span of a patient with chronic lymphatic leukemia, since the natural evolution of the disease is at times so slow that comfortable, long survival may very well occur.

Because of the facility of handling and preparation, minimal exposure of personnel, and ease of self-administration by the patient, it is suggested that the oral route of P^{32} therapy is more economical and practical than the intravenous route.

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THE CARCINOGENIC ACTION OF BENZIDINE

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THE fact that several hundred cases of cancer of the urinary bladder have been reported among certain groups of workers in the synthetic dye industry indicates the importance of this neoplasm as an occupational disease.^{12,13} Although a wide variety of dyes and dye intermediates were originally indicated as capable of inciting these cancers, it is now apparent that the etiological agents fall into the category of dye intermediates known as the aromatic amines. Moreover, of the suspected group, β -naphthylamine has been definitely proved experimentally to be capable of producing bladder cancer in dogs,^{4,14} whereas tumor production in animals by benzidine has apparently not been accomplished.¹¹ Clinically, the position of benzidine as a causal agent has also been controversial, since, in human cases of bladder cancer ascribed to the effect of this compound, clear-cut evidence has been lacking chiefly because men exposed to benzidine had also frequently been exposed to β -naphthylamine.

Therefore, when an experimental study was undertaken some years ago in an attempt to clarify in some measure the industrial-bladder-tumor problem in humans, the action of benzidine was of particular interest. This paper is concerned with the results of the investigation of the behavior in laboratory animals of benzidine and also of groups of compounds that are either encountered during its manufacture (azoxybenzene, hydrazobenzene and benzidine sulfate) or are closely allied to it chem-

ically (tolidine, azobenzene, and benzidine disulfonic acid).

RAT EXPERIMENTS

Strain. The rats were descendants of the Sherman strain, acquired from Rockland Farms, and, at the beginning of the experiments, all were about 2 months of age. These animals were kept about two weeks or until their weight was 150 gm. before administration of the chemicals was begun. Both sexes were represented in the benzidine experiments, but there was a preponderance of females early in the study because of ignorance of the greater vulnerability of males to hepatic damage.

Diet. A so called normal diet, of which the rats consumed about 10 gm. daily, was used in the standard experiments; this consisted of Purina Laboratory Chow of which the ingredients are stated to be: meat meal, dried skimmed milk, wheat germ, fish meal, liver meal, dried beet pulp, corn grits, oat middlings, soy-bean oil, dehydrated alfalfa meal, molasses, animal-protein-factor supplement, riboflavin supplement, dried brewers' yeast, thiamine, niacin, vitamin-A and -D feeding oils, vitamin-D activated plant sterol, 1 per cent steamed bone meal, 0.5 per cent iodized salt, 0.02 per cent manganese sulfate. Water was allowed ad libitum. In some of the experiments, the so-called basal diet was used; this consisted of brown rice plus 1 gm. of raw carrot daily, with no limitation of water. On the normal diet, the control and experimental animals often reached a maximum weight of 250 to 280 gm. within six months and seldom weighed less than 220 to 230 gm. even at the time of death. On the basal diet, animals rarely reached a weight of 200 gm., and often weighed less than 150 gm. at death.

From the Memorial Center for Cancer and Allied Diseases, and the National Aniline Division of the Allied Chemical and Dye Corporation

The authors wish to express their appreciation to Dr. C. P. Rhoads, Director of the Memorial Center for Cancer and Allied Diseases, for his continued interest and help, and to Dr. K. Sugimura and Mr. Bernhard Mecke for their assistance in this work.

Received for publication, May 25, 1950

Methods of Administration of Chemicals. Benzidine, benzidine sulfate, azoxybenzene, hydrazobenzene, orthotolidine, and benzidine disulfonic acid were furnished for these experiments by the National Aniline Division of the Allied Chemical and Dye Corporation. All of these compounds were of a technical quality except benzidine, which was supplied both in technical grade and in an especially purified form. Since the rats refused food containing benzidine, the chemicals were given by injection in all rat experiments except those with benzidine sulfate, which was both fed and injected. Subcutaneous injections were made in the back once weekly throughout the life of the animals until grossly obvious tumors appeared, unless contraindicated by loss of weight or obvious illness. Olive oil of a good commercial grade was chosen as the vehicle, and suitable control experiments were run parallel to the others. Some of the experiments were also duplicated with butyl succinate as the solvent, but since no differences were noted, these were not considered separately. The chemicals were dissolved so that 1 cc. of the vehicle contained the amount required for weekly injection.

At the beginning of each experiment, crude tolerance tests were run on a few animals to determine the acute toxicity, and an arbitrary dosage was established simply on a basis of short-term survival. Since the

aim of the experiment was for the maximum long-term survival, dosages were subsequently adjusted and vacation periods allowed, depending on the reaction of the animals. In general, the animals were allowed to die spontaneously. However, since several animals were kept in a single cage, those showing gross evidence of the presence of a tumor and signs of imminent death were killed to avoid cannibalism. A summary of the average and cumulated final dosage related to survival is noted in Table 1.

RESULTS

Control Series. The survival of the Sherman rat under the circumstances of these experiments on the normal diet alone was a minimum of 492 and a maximum of 1016 days, with an average of more than 600 days; on the basal diet, used only in a few corollary experiments, the minimum was 286 days and the maximum, 445 days. The basal diet itself was not productive of cirrhosis. With the group receiving olive oil alone, there was a 22 per cent mortality in the first 200 days of the experiment without definite cause except that the quarters were not air-conditioned and animals of other groups also died during this period of hot weather. Otherwise, animals in the control group receiving only olive oil and butyl succinate behaved in a way comparable to the diet-control group.

Three major diseases were responsible for death in the control series and these also accounted for death of many of the experimental animals. Tracheobronchitis with associated abscesses of the lung caused the death of the largest number of animals. Many of the animals also had otitis media and interna and a high terminal incidence of meningitis and brain abscess, with no evidence of neoplasm. In the females, pyometrium was a common finding, and, frequently, females died of acute peritonitis secondary to the infection of the uterus. A fourth, less frequent cause of death was that of paratyphoid infection in which, in

TABLE 1
DOSAGE AND SURVIVAL OF RATS

Compound	Av. amt. inj. per week mg.	Max. cumu- lated amt. gm.	Total no. rats	Survival in days		
				Less than 200	Less than 300	More than 300
Olive oil*	910	92.82	50	10	11	28
Technical benzidine	15	1.28	233	113	84	36
Pure benzidine	15	0.96	152	66	62	24
Benzidine sulfate	15	0.94	153	89	59	5
Azoxybenzene	40	4.2	66	25	4	37
Azobenzene	30	3.1	50	9	4	37
Hydrazobenzene	60	6.4	52	16	5	31
Orthotolidine	60	5.5	105	43	14	48
Benzidine disulfonic acid	20	2.8	59	11	5	43

* 910 mg. = 1 cc., and 92.82 gm. = 102 cc. olive oil.

addition to the enteritis, typical focal necroses were noted histologically in the liver and spleen.

The incidence of spontaneous tumors in the Sherman rat appears to be lower than that reported by Bullock and Curtis but greater than that in the colony reported by Ratcliffe. A motley of spontaneous benign and malignant tumors occurred in fifty-six (9.7 per cent of 578 rats); these did not include subcutaneous fibromas and sarcomas at the site of injection. Included in this group are 490 rats not otherwise incorporated in this report, and the eighty-eight previously mentioned rats in the diet- and vehicle-control groups. These spontaneous tumors comprised frequent mammary fibroadenomas, a few mammary carcinomas, occasional squamous papillomas of the forestomach, uterine and thyroid carcinomas, osteogenic sarcomas, thoracic lymphosarcomas, and generalized histiocytoses of the type found spontaneously in mice.¹⁰ Intestinal carcinomas, hepatomas, and squamous carcinomas of the skin or of other sites did not occur in any of the control animals.

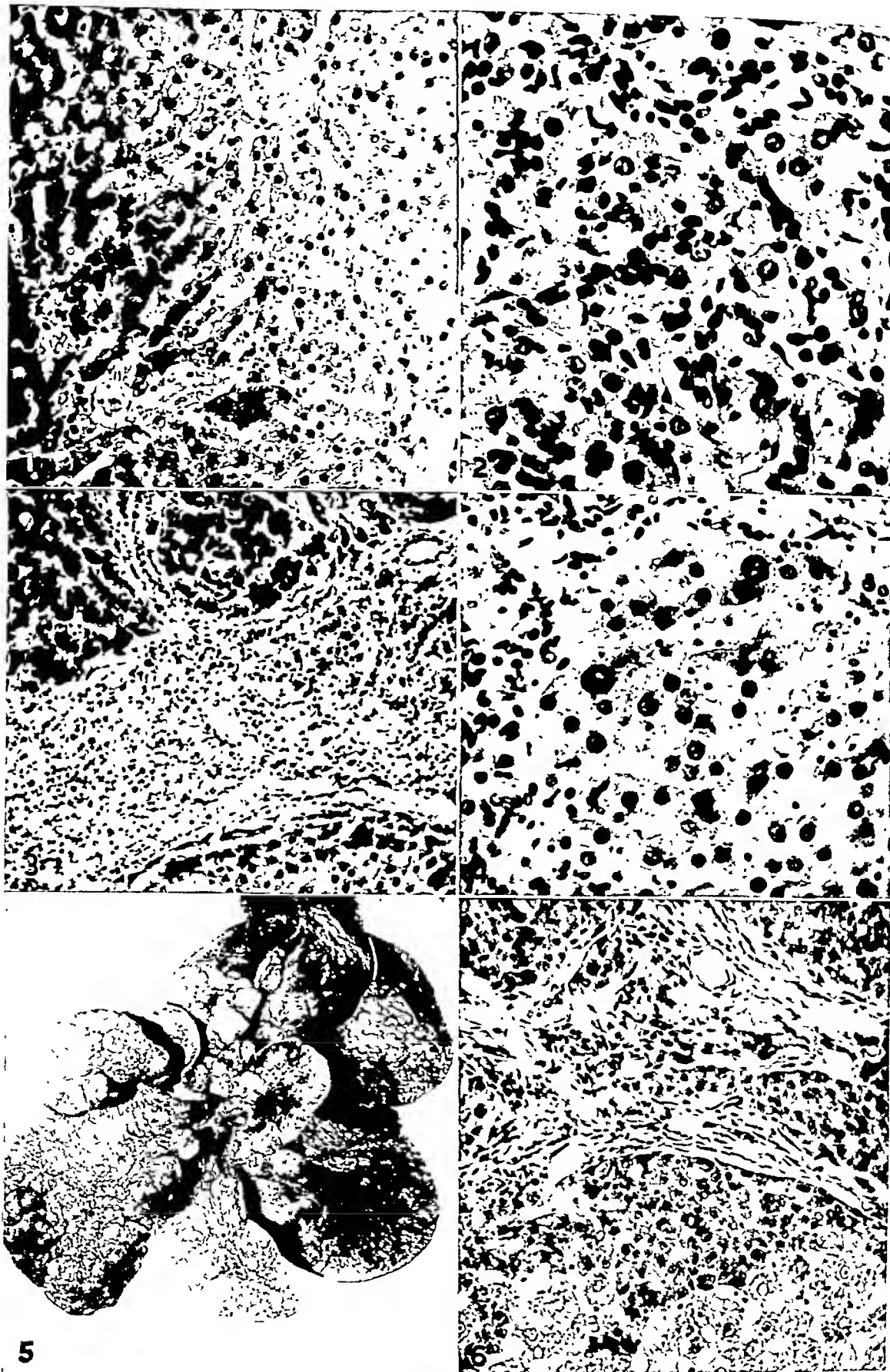
Experimental Series. Three types of carcinoma occurred in the experimental animals that seemed to indicate the carcinogenicity of benzidine; these were hepatomas, carcinomas arising in the specialized auditory sebaceous glands, and adenocarcinoma of the colon. In addition to these, ninety-two (6.2 per cent) of the 1489 rats used in these experiments bore tumors of type and distribution similar to those occurring spontaneously in the control series. It was considered that their incidence was therefore unrelated to the administration of the putative carcinogens, especially since, except for the histiocytoses, which generally occurred within the first 200 days of the experiment, these tumors occurred mainly in rats surviving beyond the time in which induced tumors usually appeared. For these reasons, the miscellaneous tumors were not included in the calculations of cancerogenic activity.

HEPATIC LESIONS

Cirrhosis. Administration of benzidine and benzidine sulfate parenterally, as well as the latter by mouth, was followed by cirrhosis in rats fed a normal diet in almost all of those surviving more than a month, and later by hepatomas in a small percentage of the animals. The related compounds, azoxybenzene, azobenzene, hydrazobenzene, orthotolidine, and benzidine disulfonic acid did not produce hepatic lesions.

The earliest deaths following administration of benzidine and benzidine sulfate occurred within forty days, and histological evidence of hepatic damage was apparent at this time although, grossly, the livers were not unusual except for pallor. Surrounding the central hepatic vein, the lobular cords were narrowed, the cells shrunken, the nuclei smaller than normal, and the sinusoids widened. The size of cells at the periphery of the lobule surrounding the portal areas was increased, the cytoplasm basophilic, and the nuclei irregularly enlarged and hyperchromatic (Fig. 1). Occasional groups of cells near the portal areas appeared to be clustered into distinct small nodules. At this early period, foci of polymorphonuclear leukocytes were noted about the portal areas and within the sinusoids. In contrast to the findings with some other hepatic carcinogens, there was no notable increase in visible lipids in this or any other stage of these experiments.

From the middle of the second month and progressively thereafter, evidence of cirrhosis and the so-called nodular regeneration were found. Within the period of forty to one hundred days, there was proliferation of fusiform cells that seemed to arise in the sinusoids and spread out to involve both the portal and central zones of the lobules and to surround and compress the isolated, often pyknotic, hepatic cells (Fig. 2). Ramifications of the small bile ducts were prominent. The lobular architecture was by this time considerably distorted; instead of normal lobules, there



(For captions see opposite page.)

were irregularly scattered hyperplastic nodules (Figs. 3, 4) composed of enlarged basophilic cells arranged haphazardly rather than radially from the central veins. In some areas, these were separated by the cirrhotic areas, and, in others, the hyperplastic nodules were almost contiguous, separated only by a very narrow zone of necrotic hepatic cells about the central vein. Grossly, the surface of the liver was often coarsely granular because of these nodules.

There was some variation in the degree of cirrhosis in individual animals; in general, the females seemed to show less severe hepatic reaction than the males. In spite of the fact that the administration of the compounds continued throughout the life of the animals, after 100 days the evidence of hepatic damage was overshadowed by the compensatory progression of the nodular "regenerative" hyperplasia. The hyperplastic nodules rarely showed necrosis such as occurred in the original parenchyma. In other words, despite the continued administration of the toxic agent, the cells of the hyperplastic nodules seem not to be sensitive to damage as were the cells of the original lobules. Eventually, the entire liver was composed of nodules separated by narrow bands of collagenized fibrous tissue (Figs. 5, 6). There was dissociation of the architectural pattern; single nodules often occupied the space of several normal lobules and at times contained multiple portal radicals and hepatic veins. In the smaller nodules, there was the same tendency for the portal veins to be central and

the central veins peripheral as noted in other types of experimental cirrhosis.¹

The cells forming the nodules were enlarged both because of increased nuclear size and increased amounts of cytoplasm, which seemed progressively to lose its basophilia. The sinusoids of the nodules were irregularly compressed and tortuous, and the Kupffer cells contained yellowish-brown pigment, some of which stained for iron. The grossly nodular appearance of the liver from 150 to 200 days reflected this structure (Fig. 5); at times, the nodules were as large as 1 cm., and some were pale and discrete enough to be grossly suggestive of neoplastic nodules.

Except for isolated instances, the degree of cirrhosis and nodularity was less severe after approximately the two hundredth day. A considerable number of livers showed lobules in which the normal radial sinusoidal arrangement was present, although all of these also showed architecturally distorted hyperplastic nodules indicating definitely at least some previous damage. Under the circumstances of these experiments, in which the aim of long-term survival was not to be jeopardized by surgical biopsy, it was not possible to determine whether the cirrhosis had undergone retrogression with recovery of the normal pattern or whether those animals surviving the longest simply had never suffered hepatic damage as severe as those succumbing at an earlier period.

In the occasional liver that retained evidence of cirrhosis at a late stage, the hyperplastic nodules were at times separated by

FIG. 1. Early hepatic damage at center of lobule with beginning hyperplasia at periphery; benzidine rat, thirty-nine days.

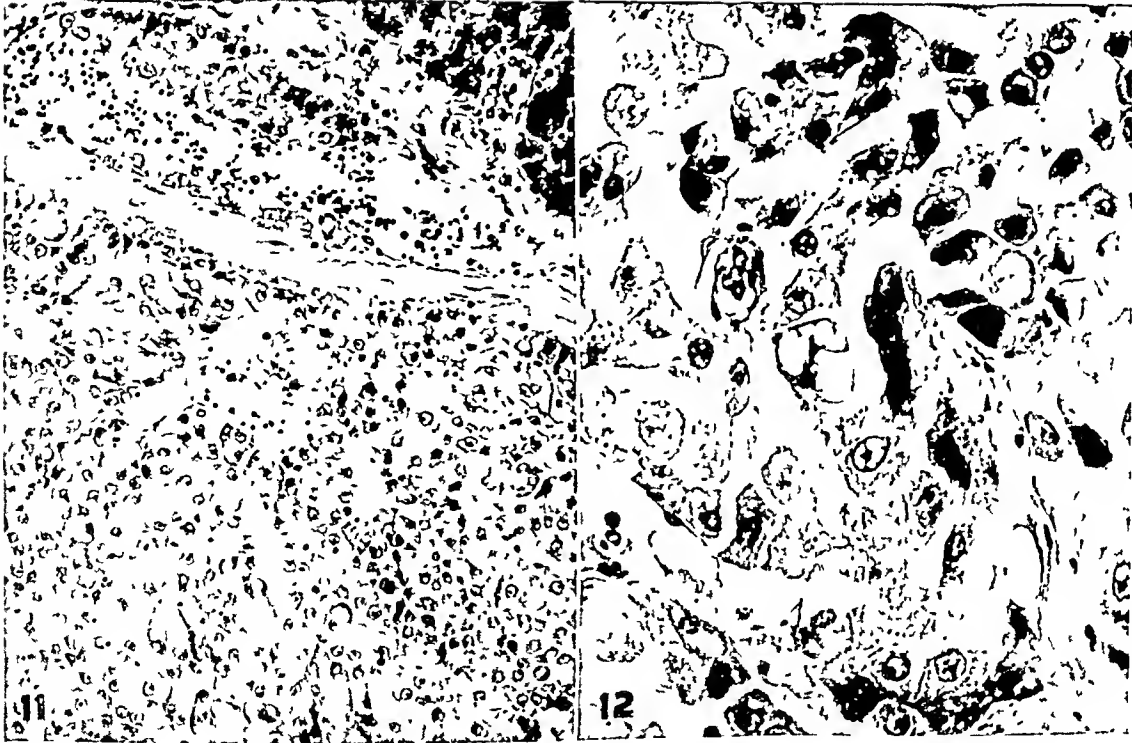
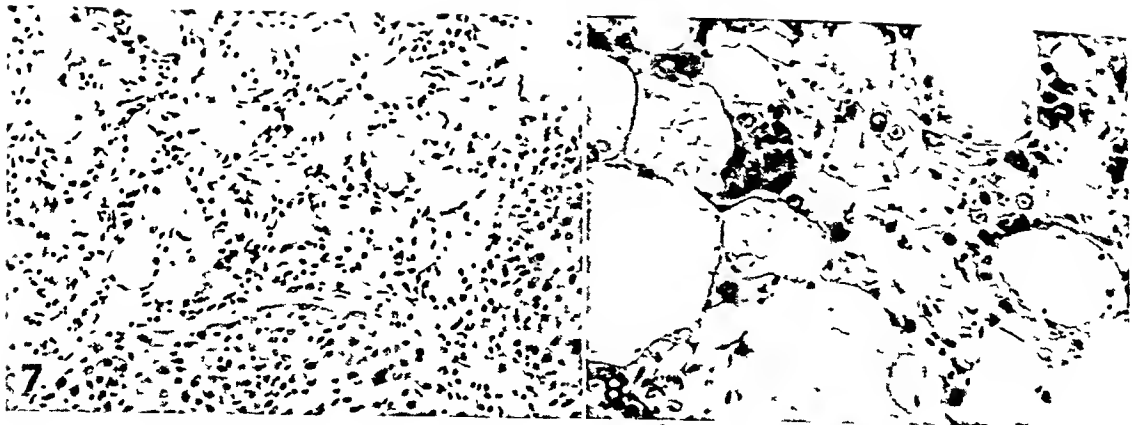
FIG. 2. Proliferation of fusiform cells around isolated hepatic cells; benzidine rat, forty-two days.

FIG. 3. Distorted hyperplastic nodules in cirrhotic liver; benzidine rat, forty-eight days.

FIG. 4. Higher magnification of one of the hyperplastic nodules shown in Fig. 3.

FIG. 5. Nodular liver; benzidine rat, 166 days.

FIG. 6. Hyperplastic distorted nodules of liver separated by narrow septa of fibrous tissue; benzidine rat, 166 days.



(For captions see opposite page.)

TABLE 2
INCIDENCE OF HEPATOMAS
Normal Diet

Compound	No animals	Male		Female		Earliest appear tumor (days)	Total no hepatomas
		No	Hepatomas	No	Hepatomas		
Technical benzidine	233	78	8 (9.8%)	155	0	264	8 (3.4%)
Purc benzidine	152	45	5 (11.1%)	107	1 (0.9%)	245	6 (3.9%)
Benzidine sulfate (inj.)	153	—	—	153	1 (0.65%)	261	1 (0.65%)
Benzidine sulfate (fed)	37	3	1 (33%)	34	0	536	1 (2.7%)
Azoxybenzene	66	—	—	66	0	—	—
Azobenzene	50	—	—	50	0	—	—
Hydrazobenzene	52	—	—	52	0	—	—
Orthotolidine	105	—	—	105	0	—	—
Benzidine disulfonic acid	59	—	—	59	0	—	—

large fibrotic wedges in which were contained a number of small, but distinctly dilated, ducts (Fig. 7). It was noteworthy that, quite unlike the experience with butter yellow in which large cysts appear regularly,¹⁵ macroscopic cysts formed from proliferated bile ducts failed to occur after the use of benzidine. After about the two hundred fiftieth day, however, microcysts of another type were seen in most of the livers. These seemed to be derived from the sinusoids that were dilated by blood or fibrinous fluid (Fig. 8). These cysts were most common in the hyperplastic nodules and were similar to small cysts also present in the hepatomas to be described later.

Hepatic Tumors. Whereas neither cirrhosis nor hepatic tumors developed in experiments with the various compounds related to benzidine except benzidine sulfate (Table 2), fourteen (3.65 per cent) fully developed hepatomas occurred in the combined group of 385 rats fed a normal diet

that comprised the technical and purified benzidine injection experiments. The earliest of these occurred at 245 days, and the great majority occurred after the three hundredth day of the experiment. Only one hepatoma occurred after the feeding of benzidine sulfate as well as after the injection of the same compounds. Since the cirrhosis developing in these animals was of the same general degree as that following benzidine administration, the fact that all animals in the benzidine sulfate injection experiments were female was considered as a likely explanation of this discrepancy. It seemed evident (Table 2) throughout these experiments that the males were far more likely to develop hepatic tumors than the females and, as mentioned before, females in general seemed to show less severe hepatic damage. Of fourteen hepatomas noted in the benzidine experiments, only one was found in 262 females (0.38 per cent), while thirteen occurred in 123 males (10.5 per

FIG. 7. Slightly dilated bile ducts in fibrotic wedge separating hyperplastic hepatic nodules; benzidine rat, 194 days.

FIG. 8. Parenchymal cysts in hyperplastic nodule of liver; benzidine rat, 252 days.

FIG. 9. Small hepatomas, histologically of trabecular type; benzidine rat, 264 days.

FIG. 10. Two histologically malignant hepatomas; benzidine rat, 327 days. Note the grossly smooth surface, except for the tumors, in this liver as well as that of Fig. 9.

FIG. 11. Trabecular hepatoma showing invasion of endothelial-lined channel at the periphery; benzidine rat, 252 days.

FIG. 12. Malignant hepatoma; benzidine rat, 327 days.

cent). No morphological changes were noted in the endocrine organs of either sex. It is interesting to note the similarity in the sex distribution of hepatic tumors caused by benzidine and that of hepatic tumors produced by acetylaminofluorine.^{3, 7}

GROSS APPEARANCE OF HEPATIC TUMORS. Grossly, the livers containing hepatomas were rarely diffusely nodular; the surface was generally smooth and pale except for the protrusion of the tumor nodules (Figs. 9, 10). In all instances, there were multiple, grayish-white, soft tumor nodules, located commonly on either the dorsal or ventral aspects of the large left lobe. In several of the livers, hepatomas were histologically identified that were less than 1 cm. in diameter and grossly had an appearance similar to the pale hyperplastic nodules that were so common in the livers of rats surviving more than 250 days. The death of these rats showing small hepatomas was related to sepsis associated with cancers occurring adjacent to the auditory canal rather than to the hepatic lesions. These cancers are to be described shortly.

As a rule, the hepatomas varied from 2 to 4 cm. in diameter and remained well demarcated from the surrounding parenchyma regardless of their size. Central necrosis was evident in all that reached a diameter of 2 cm. In four of the fourteen tumors, multiple metastatic nodules were present in the omentum, but metastases to other organs were not noted.

HISTOLOGICAL APPEARANCE OF HEPATOMAS. The structure of the hepatic tumors following the administration of benzidine was in most respects quite like those produced by butter yellow.^{8, 15, 16} In this small group of fourteen, at least one of the multiple tumor nodules in twelve of the rats had the histological appearance of malignant hepatoma, with other nodules of "trabecular hepatoma"; two of the livers showed only trabecular hepatomas. One major difference of the benzidine tumors from those of butter yellow was that adenocarcinoma

(cholangioma) did not occur; there were foci in the histologically malignant hepatomas strongly suggesting a glandlike arrangement, but this appearance was more like the acinar formation derived from hepatomas⁸ than true adenocarcinoma.

The "trabecular hepatoma"¹⁵ or Hepatoma Type I⁸ was the most common of this group, since it occurred alone and, in addition, as separate tumors in livers that also contained malignant hepatomas. The structure was that of irregular, broad, but fairly orderly, trabeculae of large acidophilic cells, in which the nuclei were often irregularly enlarged and hyperchromatic and the nucleoli were unusually prominent (Fig. 11). The trabeculae varied from two to twenty or more cells in thickness and were separated by narrow sinusoidal channels and occasional, wide septa. The marginal cells of these columns were palisaded, and their nuclei were lined up along the bordering sinusoids. While these tumors were generally grossly discrete, small rounded projections often extended into the surrounding parenchyma. Invasion of venous channels at the periphery of the tumors was noted in several instances, but metastases were not found.

Hyperplastic "regenerative" nodules were often large in livers of the animals that had survived more than 250 days, and they were difficult at times to differentiate histologically from the trabecular hepatoma. The final differential criterion used in this study was the regular alternation of narrow columns of hepatic cells with intervening sinusoids in the hyperplastic nodules (Fig. 6), a feature missing in the hepatoma (Fig. 11). Other differential features, such as nuclear enlargement and hyperchromatism, the presence of cysts, etc., were often more marked in the regenerative nodules than in the true tumors. Use of criteria such as the absence of glycogen in the tumors, as compared with its presence in altered parenchymal nodules, was not employed in this study, since animals were allowed to die and glycogen is hydrolyzed rapidly after death.

The structure of the histologically malignant hepatoma was variable; foci resembling the trabecular hepatoma were frequently noted, but, in general, no definite columnar pattern was evident. Rather, the cells were haphazardly arranged in sheets in which there were very sparsely distributed sinusoids and fibrous septa. Acinar formation within the diffuse growth was common. The individual cells were irregular, often very large, and had pale acidophilic cytoplasm and prominent, frequently giant, nuclei (Fig. 12). Vacuoles and acidophilic inclusions were common in the cytoplasm of the neoplastic cells, and the latter were also occasionally noted in the nuclei. Large and small cystic spaces lined by tumor cells were found within hepatomas and appeared possibly to be enlargements of the "acinar" areas. In addition, foci of necrosis, hemorrhage, and thrombosis were common. The structure of the omental metastases reflected that of the primary tumor.

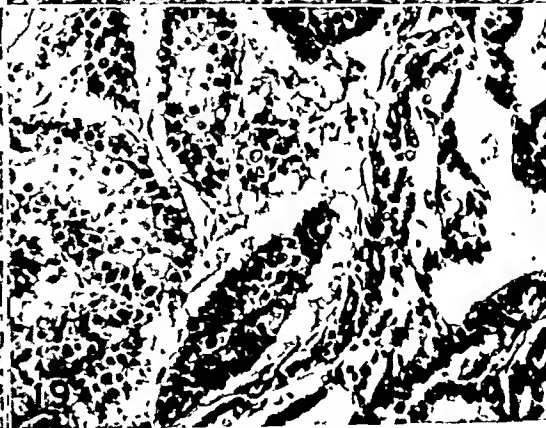
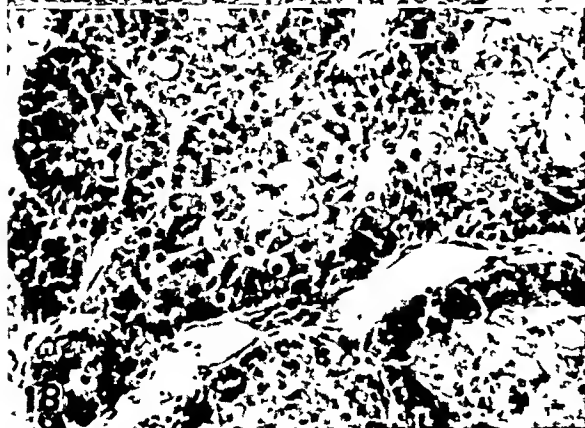
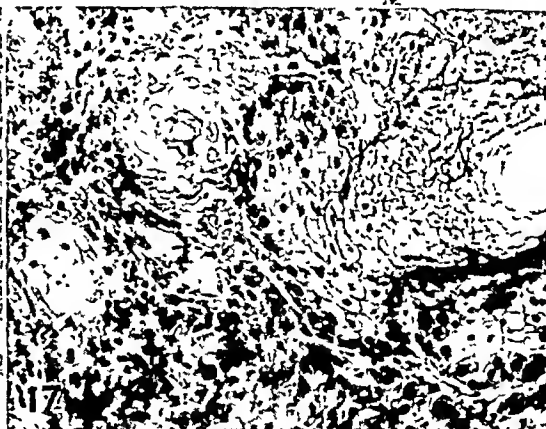
The Effect of Dietary Variations. Following the initial experience, that benzidine produced not only cirrhosis but also a small number of hepatic tumors in rats on a normal diet, it seemed feasible to make some attempt to increase or decrease this incidence by means of dietary variations. For this reason, parallel experiments were conducted with the basal diet, consisting of brown rice and carrots. The overall survival time in these groups was sharply reduced so that not a single animal survived to 300 days, and more than 75 per cent of the rats were dead before 200 days. Of 214 rats in which the cirrhosis was increased in severity and rapidity of development, only two hepatomas occurred (0.9 per cent). It was considered that, since hepatomas rarely occurred with these compounds at less than 300 days in rats on a normal diet, the negative results of the experiment were related to shortened experimental time and possibly to sharp reduction in amount of compound tolerated rather than to other factors. In addition,

other substances were added to the normal and basal diets in an effort to alter the incidence of hepatic tumors. When brewers' yeast, riboflavin, casein, or liver powder was administered to individual groups of rats receiving benzidine injections and the "normal diet," an increased incidence of hepatomas did occur: in 195 rats, there were fifteen hepatomas, an incidence of 7.7 per cent as against 3.6 per cent in those on normal diet without supplements. On the other hand, in experiments in which the same substances were added to the basal diet, two hepatomas occurred in 175 rats, an incidence of 1.1 per cent. Differences in survival time comparable to those mentioned before probably also accounted for this disparity in incidence, since the sexes were practically equally divided in these groups.

TUMORS ARISING ADJACENT TO THE EXTERNAL AUDITORY CANAL

The most common tumor occurring in this group of experiments was one appearing beneath skin just below and slightly anterior to the orifice of the external auditory canal. In the majority of instances, this tumor had the histological appearance of a keratinized squamous-cell carcinoma. Such a carcinoma has been previously mentioned as occurring in animals on feeding experiments with acetylaminofluorine.^{3, 19} The precise histogenesis of this neoplasm requires clarification.

A total of fifty-four such cancers was found among the 233 animals injected with technical benzidine (23 per cent), and thirty-two occurred in 152 animals injected with pure benzidine (21 per cent) under conditions of the normal-diet regimen. In the feeding of benzidine sulfate, the incidence was reduced in comparison to the injection of the same compound; sixteen occurred among 153 injected rats (10.5 per cent), and only two were found in thirty-seven rats of the feeding experiment (5.4 per cent). This tumor also occurred in five relatively old rats of the 105 injected with orthotolidine



(For captions see opposite page.)

TABLE 3
INCIDENCE OF CARCINOMAS ARISING IN
SEBACEOUS GLANDS OF THE
AUDITORY CANAL

Compound	No animals	Route	Earl est appear tumor (days)	Total no tumors
Technical benzidine	233	inj	190	54(23.0%)
Pure benzidine	152	inj	188	32(21.0%)
Benzidine sulfate	153	inj	229	16(10.5%)
Benzidine sulfate	37	fed	239	2(5.4%)
Azobenzene	66	inj	—	0
Azobenzene	50	inj	796	1(2.0%)
Hydrazobenzene	52	inj	366	1(1.9%)
Orthotolidine	105	inj	354	5(4.3%)
Benzidine disulfonic acid	59	inj	—	0

(4.3 per cent), while only a rare instance was seen with azobenzene and hydrazobenzene, and none with azobenzene and benzidine disulfonic acid (Table 3).

At the time of death, the majority of rats with these carcinomas were between 200 and 300 days following the beginning of injection of benzidine: the earliest at 190 days and the average at about 290 days. The average time of occurrence in the pure benzidine and benzidine sulfate experiments was somewhat later. Approximately 80 per cent of animals in the benzidine experiments developed this carcinoma if they survived beyond 250 days. Most were unilateral, with fairly equal distribution between the right and left sides; 10.6 per cent were bilateral. No sex difference was noted in the occurrence of this tumor.

These squamous cell carcinomas were first noted on examination approximately one month before the death of the animal and were actually responsible for death in many instances, inasmuch as ulceration

through the skin and subsequent infection led to meningitis or brain abscesses; occasionally, death resulted from pulmonary metastases. Attempts to prolong the life of animals by administration of antibiotics in order to increase the incidence of hepatic tumors were not successful.

At the time of discovery of these tumors, they appeared as small subcutaneous nodules, 4 to 5 mm. in diameter, over which the skin was at first freely movable, but they were attached to the lateral aspect of the underlying tympanic bulla of the skull. The growth was rapid, so that within two weeks the nodule often measured as much as 2.5 cm. and was ulcerated through the overlying skin (Fig. 13), as well as into the external auditory canal. The rats did not live more than one to two weeks beyond this period. Rarely, the tumors became so large that the entire neck was enlarged and grossly infiltrated with neoplastic tissue. On gross dissection, the surface of the tumor before ulceration (Fig. 14) was lobulated, soft, grayish white, and encapsulated; on cross section, all were irregularly cystic and contained grumous material.

In order to determine the morphogenesis of this tumor, a separate group of twenty rats was injected with technical benzidine and sacrificed at intervals beyond the one-hundred and fiftieth day, or as soon as a nodule appeared. This group has not been included in the statistical calculations. The head was amputated at the level of the lower cervical vertebrae and fixed in 10 per cent formalin after stripping away the skin.

FIG. 13. Late ulceration of squamous carcinoma arising from specialized sebaceous glands adjacent to external auditory canal; benzidine rat, 274 days.

FIG. 14. Encapsulated subcutaneous sebaceous-gland tumor, necrotic tumor protruding from ear is due to invasion of auditory canal; benzidine rat, 264 days.

FIG. 15. Cross section of head of rat killed when tumor first palpated below ear, showing encapsulated nodule at left in relation to auditory canal; benzidine rat, 181 days.

FIG. 16. Large, specialized sebaceous gland adjacent to auditory canal; normal rat, 100 days.

FIGS. 17, 18, and 19. Variations in the histological appearance of carcinomas arising in the sebaceous glands adjacent to the auditory canal.

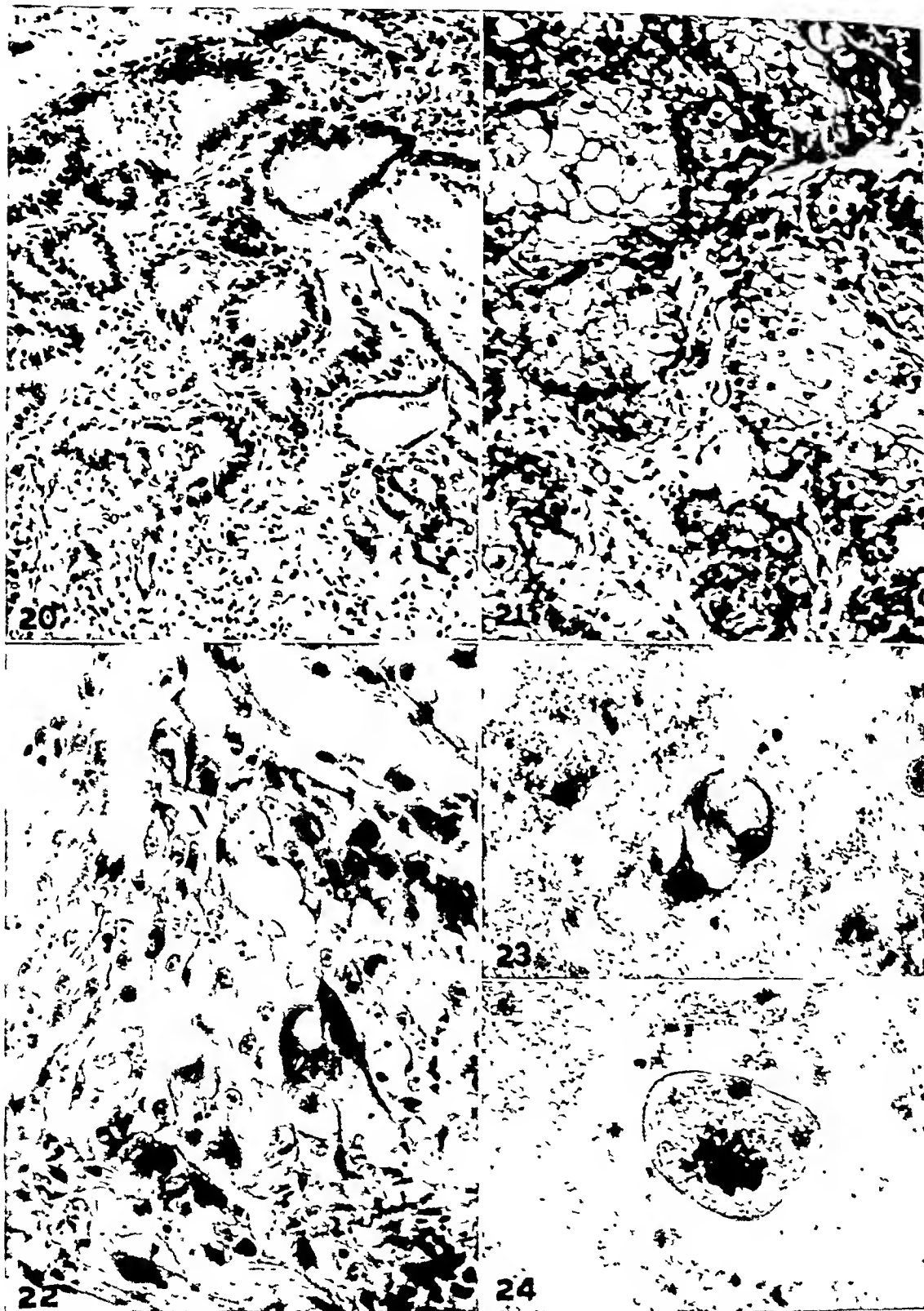


FIG. 20. Adenocarcinoma of rectum; benzidine rat, 303 days.

FIGS. 21 and 22. Low- and high-power magnification of papillary epidermoid carcinoma of bladder; benzidine dog, ninety months.

FIGS. 23 and 24. Abnormal cells recovered from urine of benzidine dog having carcinoma of bladder shown in Figs. 21 and 22.

The entire skull was then decalcified in 10 per cent nitric acid, and serial blocks 2 mm. in thickness were cut, imbedded in paraffin, and sectioned. Later, serial sections were cut from some blocks to trace more precisely the origin of the lesion (Fig. 15).

In normal rats, mice, and some other rodents, there has been demonstrated^{20, 21} a specialized sebaceous gland, located beneath the skin and the medial parotid gland, between the external auditory canal and the tympanic cavity, which differs from the many small sebaceous glands of the external auditory canal in that it is much larger and does not bear hairs. The normal gland is visible as a small yellow nodule, at times as large as 3 to 4 mm. The histological appearance is that of a typical sebaceous gland, lacking hair, arranged in three or more large lobes (Fig. 16). Communication with the external auditory canal is by way of a single duct that is lined by stratified squamous epithelium and enters the canal between its osseous and cartilaginous portions just external to the tympanic membrane.

In the early phase of the development of the tumors derived from these glands, there was residual evidence of the sebaceous nature of the tumor (Figs. 17, 18). Even in this early phase, however, the keratinization of the tumor generally overshadowed the sebaceous elements (Fig. 17). After the tumor was grossly visible, there was often no indication of its sebaceous nature except for the large amounts of fat consistently present. There was great variation in the appearance of the tumors; most were mature, keratinized squamous-cell carcinomas, others were less differentiated (Fig. 18), and some were combined with true glandular elements (Fig. 19). Careful investigation of all the salivary and lacrimal glands in the area of these tumors, however, failed to indicate any participation of these glands in the formation of the tumors noted even when glandular structure was evident. Salivary-gland tumors were not found.

The fact that a few of these carcinomas occurred in compounds related to benzidine

(Table 3) is difficult to explain, since these same compounds seemed to have no other carcinogenic significance. The possibility that this type of tumor may occur spontaneously in the Sherman rat has been considered, but instances have not been noted in control animals.

ADENOCARCINOMA OF THE COLON

Seven instances of adenocarcinoma of the rectum have occurred among the 385 rats injected with benzidine; all of these occurred in males, 200 or more days after injections were begun. These carcinomas arose at the junction of the rectum and colon, generally encircled and involved 1 to 2 cm. of the length of the gut, and extended through the wall into surrounding tissues; no metastases were noted. Histologically, these carcinomas were of the typical glandular arrangement of cells containing mucus (Fig. 20) similar to human intestinal cancer, and all showed large gelatinous areas that were visible even grossly. The fact that the occurrence of intestinal cancer was confined to males in these experiments also coincides with experience with acetylaminofluorine.³ Adenocarcinomas of the intestinal tract did not occur in experiments with related compounds nor in any of the control series.

APPEARANCE OF THE URINARY BLADDER IN RATS

The urinary bladders of all the rats used in these experiments were studied histologically. The bladder was usually found distended at the time of postmortem examination, and the urethra was therefore tied with cotton thread before removal of the organ from the body. The distended bladder was then fixed in formalin, and folds, which seem to have led to erroneous interpretations in the literature, were eliminated as a problem in this study.

The incidence of the nematode, *Trichosomoides crassicauda*, was high in the bladders of these rats; cross sections of the worms were seen within the mucosa of more than half the entire series of experimental

and control animals. In no instance was there evidence of any reaction whatever of the mucosa to the presence of the worms. Moreover, in only two animals were there lesions of any kind in the bladder; these two had multiple small stones, and worms were not seen. Neither papillomas such as those reported in the presence of the nematodes¹⁸ nor tumors of any kind were found.

MONKEY AND RABBIT EXPERIMENTS WITH BENZIDINE

Four female monkeys (*Macacus rhesus*) received subcutaneous injections with 50 to 200 mg. of benzidine in butyl succinate weekly for periods of two to nearly five years, with cumulative dosage amounting to 6.2 to 9.1 gm. One died at twenty-six months, the others at forty-nine, fifty-eight, and sixty-two months respectively, mainly of respiratory infections. Examination of all viscera, including multiple sections of the entire bladder, failed to reveal evidence that benzidine had any effect on these animals.

Twenty-two female rabbits were injected weekly with 75 to 150 mg. of benzidine in olive oil, subcutaneously, with total cumulative dosage varying from 0.75 to 6.8 gm. Half of these animals died within the first hundred days of the experiment and the average survival of the remainder was in the neighborhood of 300 days, although three rabbits lived more than 500 days. No evidence of significant lesions was noted in the viscera of any; continuation of the experiments with rabbits was halted because of the difficulty in prolonging sufficiently the survival time, particularly since, in the series of Berenblum and Bonser, rabbits received more than twice this amount of benzidine and survived longer with negative results.

EXPERIMENTS WITH DOGS

Seven mongrel dogs, weighing about 25 pounds each, one male and six females, have been fed benzidine for a period of

five years. The bitches were full grown when started on the experiments, and it was desirable that they had borne at least one litter in order to facilitate cystoscopy. The administration was accomplished by the feeding, six days each week, of capsules containing 200 mg. of benzidine for fifteen months, and 300 mg. for the next forty-five months. The dogs received, over the period of five years, 325 gm. of benzidine by mouth. The compound was well tolerated, and no signs of toxicity were noted. In addition, four female dogs have been fed benzidine sulfate under identical conditions for five years, with total dosage of more than 100 gm.; these are living in their seventh year with no cystoscopic evidence of vesical lesions.

Of those dogs fed benzidine, one of the females is dead and the remainder are alive from ninety to ninety-seven months from the beginning of the experiment. Death ensued in the one at eighty-nine months as a result of a retroperitoneal abscess apparently originating from infection in one uterine horn. No pathological effects from the administration of benzidine were noted in this animal. The bladder was normal.

The female dogs have been cystoscoped at intervals of three to four months throughout the experiment;* in addition to inspection of the bladder, biopsies have been taken whenever a lesion was noted. The male has not been cystoscoped. Recently, stained smears have been made from the urinary sediment and searched for tumor cells, but since catheterized urine is required in order to obtain a specimen clean enough for this purpose, this method was not considered any advantage over cystoscopy and biopsy, particularly since cells were often degenerated and their interpretation equivocal. This same method, however, might offer advantages over those currently used in the programs of bladder-cancer detection in the dye industry.

* We are indebted to Dr. B. S. Barringer in early years of this work and to Dr. W. F. Whitmore of the Urological Service, Memorial Center for Cancer and Allied Diseases, for performing the cystoscopic examinations.

Recurrent episodes of cystitis were noted in the bladders; histologically, the biopsy specimens showed focal collections of lymphocytes, often forming follicles, but no notable reaction of the mucosa. This lesion improved without specific therapy.

In the ninetieth month of the experiment, one dog was discovered, on cystoscopic examination, to have multiple elevated papillary tumors involving a large segment of the mucosa of the anterior wall of the bladder and similar smaller tumors scattered elsewhere on the mucosa. Biopsy of two of these showed that the grossly visible papillations were composed of thickened, keratinized epidermoid folds, in which the cells were enlarged and the nuclei irregular and hyperchromatic. Bizarre mitotic figures were noted. There was definite infiltration of some of the epidermoid nests into the underlying stroma. The histological appearance was that of an epidermoid carcinoma of the bladder (Figs. 21 to 24) similar to those produced by β -naphthylamine in dogs. Only two months have elapsed since the discovery of this carcinoma, and the dog remains in good physical condition.

The three remaining female dogs have shown no cystoscopic evidence of neoplastic disease in the bladder; nor has examination of urinary sediments yielded any unusual cells. The status of the bladder in the male is not known.

The occurrence of only one bladder cancer in a dog eight years following the beginning of benzidine feeding cannot be used as evidence for the carcinogenic action of benzidine in this species. Bonser⁵ has already reported negative results in experiments in progress for more than five years in which the dogs received by feeding as much as 700 gm. of benzidine. Moreover, spontaneous cancer of the bladder in dogs is known, although apparently very rare; Feldman quotes no cases of his own but does cite several isolated reports including the six bladder cancers in dogs among 766 carcinomas of the dog mentioned by Sticker. Since carcinoma of any organ in the dog is generally a disease of old age (the dog

in this group is at least ten years old), and since the vesical cancers induced by β -naphthylamine occur within two years following the administration of adequate amounts of the compound, a final interpretation of this finding in one dog must await the end result in five other dogs on the same experiment.

SUMMARY AND CONCLUSIONS

1. The administration of benzidine to rats was followed consistently by hepatic injury and subsequent cirrhosis similar in the late stages to portal cirrhosis of humans. Benzidine was carcinogenic for rats to the extent that sebaceous-gland carcinomas that have been demonstrated as arising from specialized sebaceous glands adjacent to the auditory canal occurred frequently, and that hepatomas and adenocarcinomas of the rectum occurred in a small percentage of the animals. Bladder tumors did not occur. The results from technical and especially purified benzidine were similar, thereby eliminating the possibility that the carcinogenic agent was an impurity in the technical compound.

2. Benzidine sulfate, administered orally and parenterally to rats, had a similar but less potent carcinogenic activity.

3. Parenteral administration of compounds related to benzidine, including orthotolidine, azoxybenzene, hydrazobenzene, azobenzene, and benzidine disulfonic acid, showed practically no effect in rats.

4. The results of administration of benzidine to rats were similar to those produced by butter yellow insofar as hepatic injury occurred early and was followed by hyperplastic nodular cirrhosis but differed from the latter in the smaller incidence and delay of appearance of hepatomas. Hepatomas and rectal adenocarcinomas occurred predominantly in males of these experiments.

5. Variations in diet failed to produce conclusive results, probably because of sharp reduction in survival span of the rats.

6. No tumors occurred in rabbits or monkeys after injection of benzidine.

7. In one of seven dogs that were fed benzidine for five years and survived from five to eight years, a papillary carcinoma of the urinary bladder was recently found on cystoscopic examination. Although blad-

der cancer is known to occur spontaneously only rarely in dogs, no conclusions concerning the carcinogenicity of benzidine for dogs may be drawn from this single occurrence.

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PRIMARY DIFFUSE TUMORS OF THE MENINGES (SO-CALLED MENINGEAL MENINGIOMATOSIS)

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SOLITARY tumors arising from the meninges are widely known and well-recognized tumors that are usually referred to as meningiomas. Multiple tumors of such origin are relatively infrequent but numerous examples have been reported in the literature. Primary diffuse tumors of the meninges, however, are rare. Necropsy has been performed recently in two such cases at the Mayo Clinic, and these two cases together with two previous cases constitute the basis of our report. The fact that these four cases were all that were found in the study of approximately 4500 tumors of the central nervous system at this clinic indicates the rarity of the neoplasm. Fifteen similar cases have been found in the literature since 1927. Cases prior to this date, in which the diagnosis was that of primary diffuse tumors of the meninges, were not included in this study because there was doubt concerning the diagnosis.

It was in 1925 that Bailey and Cushing first described medulloblastoma, a tumor frequently confused with primary diffuse tumors of the meninges; at about this same time, silver methods for impregnation that sharply distinguished reticulin from collagen became more widely used. Cases^{1, 3, 9, 12, 15, 20, 26} of diffuse involvement of the perivascular extensions of the meninges with or without diffuse involvement of the meninges over the surface of the brain are not included because it is believed that they are a part of a process different from the one under consideration. It is the simple step from extensive discrete involvement of the meninges with tumor to diffuse in-

volvement of the meninges with which our paper is concerned.

GROSS CHARACTERISTICS

Primary diffuse meningeal tumors contained in the brain and spinal cord revealed considerable variation in gross characteristics. In general, however, the arachnoid over a large portion of the cerebrum, the base of the brain, the cerebellum, the spinal cord, or a combination of any of these locations, was the site of thickening that measured up to 5 mm. in depth. Around the spinal cord, it was often appreciably thicker. The tumor usually followed the cortex even into the deeper sulci and presented a smooth, reddish aspect on the surface. The appearance has been likened to "pink icing on a cake" by several authors. In some cases, the extensive vascular supply attracted the attention of the observer, and in a few cases, there was rather extensive hemorrhage into the tumor. Owing to irregularities in the thickness of the tumor, grayish-white flecks have been noted within the diffusely thickened arachnoid and have led to a mistaken diagnosis of tuberculosis, particularly in those cases with involvement at the base of the brain. In several cases, a diffuse thickening that obscured the normal configuration of the brain was noted in association with meningiomas; in one case, several thin, plaquelike meningiomas were present, and one of them faded imperceptibly into the diffuse tumor. In still another case, the extensive neoplastic tissue was so thin that grossly a lesion was not noted. It is evident, therefore, that the diagnosis of primary diffuse tumor of the meninges cannot be established in all cases by gross examination of the brain and spinal cord, and, moreover, the gross appearance may lead to an incorrect diag-

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Received for publication, April 13, 1950.

nosis. In those cases in which it is recognized that the meninges are diffusely involved with tumor, the diagnosis of primary diffuse tumor of the meninges cannot be established until those tumors that may secondarily involve the meninges are excluded.

We have divided the cases that have been reported in the literature into various categories for purposes of discussion, particularly to indicate the existing analogies with the solitary meningiomas. In regard to the various theories of origin of the meninges, suffice it to say that we recognize two tissue components in the meninges that are involved in the formation of tumors; namely, the arachnoid cells and the connective-tissue elements. A solid, discrete tumor may arise from either component, forming thereby a meningothelial meningioma if derived from the arachnoid cells, and a fibroblastic meningioma if derived from the connective-tissue stroma. A mixed type of meningioma is the result of proliferation of both components. Malignant characteristics may develop in meningiomas arising from either or both components; in such cases, the tumor is designated as a "malignant meningioma."²³ Whether calcium is deposited in the form of psammoma bodies or whether bone is formed within the tumor is not believed to be of sufficient significance to alter this fundamental concept of origin. The tumors designated as "angioblastic" or "lipomatous meningiomas" are thought to be in separate categories and distinct from true meningiomas. As the solitary meningiomas are composed predominantly of arachnoid cells, fibrous tissue, or a combination of both, so may the multiple meningiomas be similarly constructed, and, also, one or more of them may undergo malignant transformation of either or both components. In one case, thirty-eight discrete meningiomas were present over the surface of one hemisphere of the cerebrum.¹⁷ Further evidence that these three entities: solitary meningiomas, multiple meningiomas, and diffuse meningeal tumors represent the same fundamental

process is the fact that they occur in various combinations in the same patient, such as one or more solitary meningiomas with many tiny meningiomas, or one or more meningiomas with areas of diffuse meningiomatosis in adjacent or entirely separate areas of the meninges. The most important evidence, however, is adduced from a careful study of the histological features of such cases.

From this viewpoint, the primary diffuse tumors of the arachnoid are divided into three groups: (1) those that appear to arise from the arachnoid cells; (2) those that appear to arise from the stromal cells, and (3) those that appear to be formed of an admixture of both types of cells. Only a few of these tumors have truly benign characteristics, a fact that is in marked contrast to their solitary counterpart in which most of the tumors are benign. Most of the diffuse meningeal tumors show pleomorphism of the cells, mitotic activity with bizarre mitotic figures, and invasion of the parenchyma of the brain or spinal cord. This we have taken as evidence of cancer. That these tissues are capable of reacting, and do react, diffusely in a relatively benign fashion is amply demonstrated not only by the tumors so formed but also by proliferation of the arachnoid cells seen at times in association with other neoplasms and as a part of a reaction to minimal stimulation. Benign overgrowth of connective tissue is frequently seen as a part of chronic meningitis. Sixteen cases of diffuse meningeal tumors, which we considered as probably primary, were found in the literature. These are divided into the aforementioned three categories on the basis of histological criteria alone. These criteria will be outlined subsequently.

In the literature, there are six examples^{4, 7, 10, 21} of primary diffuse tumors of the meninges that appear to have arisen from the arachnoid cap cells. The case of Lichtenstein and Ettleson is of particular interest in that the diffuse tumor was composed of large globular cells with an abundance of cytoplasm and round or oval



FIG. 1. Tumor in case 1; the characteristics of the cells are similar to those of a meningotheiomatous type of meningioma. (H. & E. $\times 912$.)

FIG. 2. One of the few small places in which the tumor in case 1 had invaded the spinal cord. (H. & E. $\times 179$.)

nuclei rich in chromatin. Although giant cells were seen in places, their nuclei were marked by the same characteristics as the globular cells, and they were considered to be the result of fusion of the cytoplasm of several cells. No mitotic figures were noted. In many places, single groups of cells hung like bunches of grapes from the arachnoid membrane. The tumor was confined entirely to the meninges with no evidence of invasion of the spinal cord, which is certainly histologically characteristic of a benign tumor, and there seemed to be no doubt of its origin from the arachnoid cells. Cases 1 and 2 reported by Casper are probably similar cases, although the description given is hardly adequate. These cases illustrated the association of solitary and diffuse meningeal tumors. One case presented several large meningiomas and the other case, one large meningioma; in addition, in each instance diffuse meningiomatosis involved the base of the brain. From these cases in which the characteristics of the tumors were entirely benign, we progress to the case of Brown and Kernohan in which the tumor showed evidence of more rapid growth. The gross and microscopic findings of this case are presented in considerable detail for comparative purposes.

REPORT OF CASES

Case 1. The clinical findings in this case of diffuse meningeal tumor of a 23-year-old man have been previously described.⁷ The pertinent findings during complete necropsy were limited to the central nervous system. Examination of the skull and brain showed the skull, dura, cerebral vessels, and venous sinuses to be normal. The arachnoid over the brain was normal except for a nodule about 5 mm. in diameter on the under surface of the left frontal lobe. The sulci and convolutions were unremarkable. The cerebellum and brain stem were not unusual except for a slight bloody tinge in the fluid of the cisterns and the fourth ventricle. Sectioning of the brain revealed slight uniform enlargement of the ventricular system. The dura of the spinal cord was distended with what was thought to be

blood. It was found, however, that a hemorrhagic tumor entirely surrounded the spinal cord and cauda equina from the level of the first thoracic vertebra to the conus medullaris. Above this level, the distribution of the tumor was irregular.

Sections of the tumor showed it to be composed of large cells with a small amount of granular, eosinophilic-staining cytoplasm that had a marked tendency to fuse with that of adjacent cells. The nuclei were large and, for the most part, oval, but some were round. The nuclei were markedly vacuolated with chromatin in several fine discrete bands. The limiting membrane was distinct, and most nuclei contained one or two rather large nucleoli. There was some pleomorphism of the cells and some mitotic figures were seen. Pyknosis of the nuclei was common. A moderate number of polymorphonuclear leukocytes were scattered throughout the tumor. Some cells tended to be arranged in long cords (Fig. 1) but most of them were in diffuse sheets. The supporting connective tissue was slight in most places, absent in some regions, but abundant in others. The tumor was confined almost entirely to the subarachnoid space, but in two tiny places, it had invaded the parenchyma of the spinal cord and in some places had involved the nerve roots (Fig. 2). In no place had it exceeded the outer limits of the arachnoid. Small groups of cells were found over the surface of the medulla, pons, and base of the brain. In these places, they showed transition with the normal cells of the arachnoid and appeared to be arising from them. In places, reticulin impregnation revealed a heavy, irregular pattern, and the reticulin seemed to be a product of the cells. Sections of the spinal cord also showed rather extensive recent hemorrhage.

As was noted previously, the tumor in this case was composed of uniform large cells with vacuolated nuclei that contained one or two large nucleoli. They closely resembled, and in several instances they appeared to be arising from, normal arachnoid-cap cells. Several focal proliferations of the cap cells were found in areas separate from the obvious tumor. It is this type of cell, which is in marked contrast to the malignant cells originating from connective-tissue stroma, that we feel has originated from the arachnoid cell.

This case presents a few bizarre mitotic figures and two small areas of invasion of

the parenchyma even though there is little pleomorphism of the large physaliferous cells. To us, this tumor represents a more rapidly growing neoplasm than that presented by Lichtenstein and Ettleson and probably corresponds to a low-grade malignant meningioma.

The case of Marchand and Picard, in which mitotic figures were frequent, pleomorphism was marked, and the spinal cord was invaded in several areas and was definitely cancerous, was similar to our case 2.

Case 2. A boy, 18 years of age, was confined to a mental institution three years before admission to the Mayo Clinic with the diagnosis of schizophrenia. He was treated with twenty-five to thirty electric shocks and was dismissed two years later. Four months before our report, he again was committed to the institution with the same diagnosis because of a delusional state. He then received about fifteen insulin-shock treatments. Two and a half weeks before admission to the clinic, weakness and numbness of the left foot and leg developed, which rapidly progressed until both lower extremities were completely paralyzed and numb. He became incontinent of urine but not of feces. During the two and a half weeks prior to his admission to the clinic, the patient also had several frontal headaches associated with severe pain over the lower left lateral portion of the thorax. These pains occurred four or five times a day and each lasted about five minutes. Examination revealed complete paraplegia with the level of the lesion at the second or third thoracic vertebra. He had bilateral acute papilledema of 4 diopters, with exudate and flame-shaped hemorrhages at the margins of the disk. Laminectomy of the first, second, and third thoracic vertebrae was performed, and a tumor was found that involved the arachnoid and extended into the parenchyma of the cord. The tumor was removed as completely as possible. The patient was apparently responding well when, on the third postoperative day, there was a sudden onset of irregular, shallow respirations, somnolence and hyperthermia, and he died.

Complete necropsy was done and, other than moderate hemorrhagic edema of the lungs, pertinent findings were limited to the central nervous system. Examination of the brain revealed the dura, cerebral



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FIG. 3. Cross section of brain, case 2, showing a nodule of tumor in the arachnoid in the circular sulcus with marked compression of the cortex. Small nodules of tumor can be seen within the lateral ventricles.

FIG. 4. Superior surface of the cerebellum, case 2, showing the slight diffuse infiltration of the arachnoid and a small mass on the left side.

arteries, and venous sinuses to be normal. A diffuse infiltration of the arachnoid with light-pink neoplastic tissue was found. It was extensive in distribution, but in general, it was a thin sheet. The tumor involved most of the surface of the cerebrum and had formed several masses that were confined to the meninges but that compressed the parenchyma of the brain. These masses were prominent in the sylvian fissures where there were several nodules of tumor measuring up to 4 mm. in diameter. A mass located in the inferior portion of the circular sulcus measured approximately 2.5 cm. in diameter (Fig. 3). It was causing marked compression of the underlying cortex and in one area was infiltrating it. This



FIG. 5. *Cervical cord, case 2, showing the extensive, diffuse involvement of the arachnoid with tumor. Note the extreme compression of the thoracic cord. (H. & E. $\times 4.5$.)*

FIG. 6. *Thoracic cord showing infarction of the remaining parenchyma. (H. & E. $\times 4.5$.)*

mass was easily enucleated and it was obvious that it had not arisen within the parenchyma of the brain. The arachnoid of the entire cerebellum and pons was diffusely infiltrated with similar light-pink neoplastic tissue that partially obliterated the normal markings. In several areas, tumor nodules were formed, the largest of which measured 2 cm. These nodules, although they compressed the cerebellum, did not invade or arise from within it (Fig. 4). Several similar nodules were noted in the diffuse tumor over the pons. The tumor extended along the entire intracranial extensions of the cranial nerves with some infiltration of them. Section of the brain showed a diffuse implantation of tumor in the ventricular system with masses measuring up to 1 cm. in diameter. Complete filling of the anterior horn of the right lateral ventricle with tumor was noted. Examination of the spinal cord disclosed it to be markedly enlarged throughout its length by diffuse arachnoidal infiltration of a similar tumor, which in places was as much as 1 cm. thick (Figs. 5, 6). There was little invasion of the spinal cord, although in the thoracic region it was extremely compressed (Fig. 6). The filum terminale was beaded with nodules of tumor measuring up to 4 mm. in diameter. Most of the cauda equina was similarly involved.

Microscopic examination revealed the tumor to be composed of large cells, each of which had a tiny rim of indistinct

cytoplasm. The nuclei were large and deeply stained. The chromatin was collected into strands or clumps resulting in a vacuolated appearance. Many cells had one or two nucleoli of medium size, and many nuclei were intensely stained so that nuclear detail could not be distinguished. Moderate pleomorphism was evident, and many mitotic figures were seen (Fig. 7). The connective-tissue stroma was quite delicate, and vascularity was not prominent. Impregnation by Perdrau's method showed abundant reticulin. Invasion of the brain and spinal cord was found in a few areas, but practically everywhere, the tumor deformed the brain and spinal cord simply by compression. In parts of the tumor, as in the mass over the cerebellum, the cells were arranged in strands or columns (Fig. 8). Immediately adjacent to such areas, there was a complete absence of pattern. Also, invasion of the cerebellar cortex was evident on the left side in Fig. 8. Invasion of the cranial nerves was rather extensive. The thoracic portion of the spinal cord was almost completely severed owing to compression by the surrounding tumor. In addition, there seemed to be recent infarction at this place probably owing to impairment of the vascular supply by the tumor (Fig. 6).

In case 2, although the cells were not so large as, and pleomorphism was more evident than, in case 1, we are of the opinion

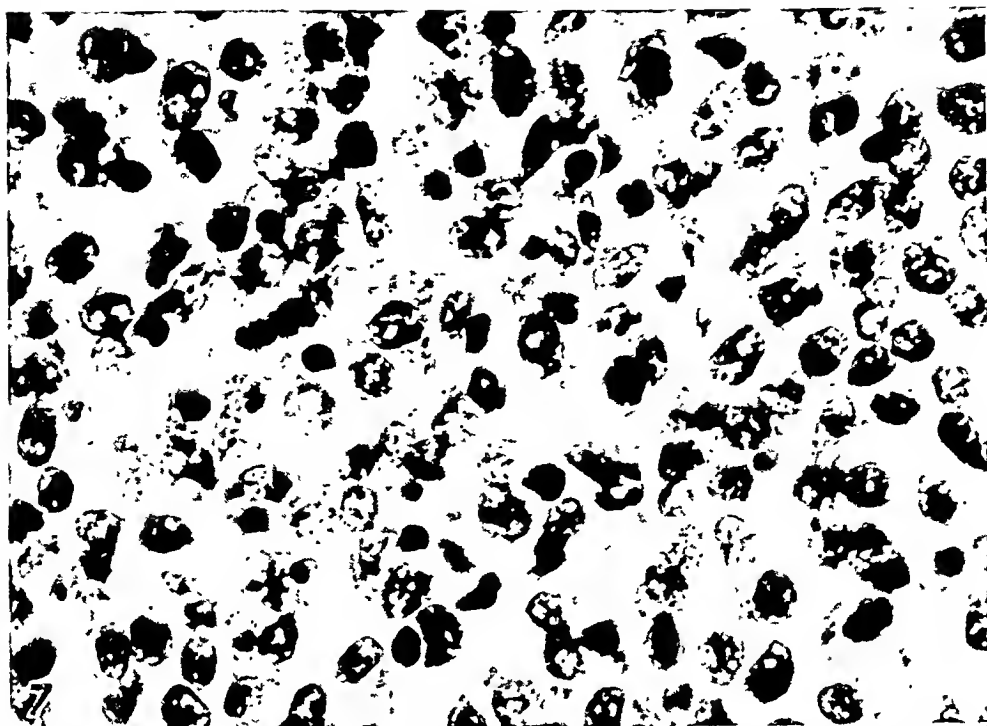


FIG. 7. Tumor, case 2, showing characteristics of the meningotheelial type of cells. (H. & E. $\times 913$.)

FIG. 8. Tumor in arachnoid of cerebellum in case 2. A well-defined pattern can be seen on the right side as compared with no pattern in the center of the photograph. A faint outline of the cortex, which is being invaded by the tumor, can be seen on the left side. (H. & E. $\times 179$.)

that the tumor also arose from the arachnoid-cap cells.

In the case of Bailey and Bucy, the tumor showed definite evidence of rapid growth with marked pleomorphism and numerous mitotic figures, but the parenchyma of the brain was not invaded. The tendency toward signet-ring formation in view of the absence of complete necrosis is disconcerting. The parallelism of these diffuse tumors with the solitary tumors originating from arachnoid cells both in respect to origin and ability to become malignant is apparent.

In the literature, six diffuse meningeal tumors were reported that appeared to originate from connective-tissue stroma.^{6, 11, 14, 16, 22} Microscopically, the cells in this type of tumor are smaller and have no cytoplasm or, at best, a tiny rim of it. They are more pleomorphic and, while they may be round or oval, they frequently assume a spindle-like shape. The nuclei are often pyknotic and the chromatin of others is dense so that it is difficult to distinguish nuclear detail. At times the arachnoid cells are not involved by the tumor. A diffuse network of reticulin is present in most areas.

The case reported by Harbitz indicates well how tumors that originate from connective-tissue stroma may have gross and microscopically benign characteristics. In their case, the cells were medium-large, round, oval, or, most frequently, spindle-shaped with fairly evenly staining nuclei of varying forms. Large amounts of collagen and reticulin were revealed by special procedures. Mitotic figures were not seen and invasion of the parenchyma of the brain was not evident. The largest of three plaquelike masses that were present was approximately 5 cm. by 4 cm. by 13 mm. and was located over the inferior portion of the sylvian fissure and the island of Reil. However, there was a diffuse tumor over the pons that was hardly perceptible, and a microscopic tumor over the cervical portion of the spinal cord. Although the involvement was not so uniformly diffuse as is seen in most of these tumors, the size of

the localized masses did not seem to be sufficient to have accounted for the diffuse spread by extension or metastasis, as is sometimes seen in perivascular sarcoma, for example. The tumor described in case 3 of Haythorn and associates, a tumor associated with a glioblastoma in the parenchyma of the brain, and that in the case of Fahr, also appeared to belong in the category of diffuse benign meningiomas of stromal type. The cases of Top and Brosius, the first case of Haythorn and co-workers, the second case of Bronfman and Reumont, and our case 3 illustrate how these tumors may have malignant characteristics.

Case 3. Two weeks before his admission to the clinic, a baby boy, 21 months of age, had a jacksonian seizure that involved the right side of his body and lasted six hours. This episode was accompanied by vomiting. After this, he seemed oblivious of his surroundings for twelve to eighteen hours. During the next week he was somewhat unresponsive and was unable to sit up, always falling to the right. A week before admission, he again had an attack of vomiting not associated with convulsions. On the day of admission, he had another episode of unconsciousness accompanied by jerking movements of the right arm. He appeared acutely ill. The head was enlarged and a "cracked pot" sound was elicited on percussion. The eyes were divergent, but the pupils were equal and reacted to light, and accommodation was normal. Moderate bilateral papilledema, nuchal rigidity, and a rhythmical tremor of the right hand were noted. The reflexes were hyperactive but equal, and abdominal reflexes were absent. During the examination, the patient had a tonic, extensor convulsion with opisthotonus and extension of both legs and the left arm but moderate flexion with clonic twitches of the right arm and vermiform movements of the fingers. Roentgenograms demonstrated a separation of the sutures of the skull. Ventriculograms revealed hydrocephalus of the lateral and third ventricles, some dilatation of the aqueduct, and some compression of the fourth ventricle. Examination of the fluid from the ventricles revealed numerous clumps of hyperchromic cells that were diagnosed as malignant. Bilateral suboccipital craniotomy was done and a diffuse tumor was found that involved the arach-



FIG. 9. *Base of the brain in case 3 showing diffuse involvement of the arachnoid and obliteration of normal markings.*

noid over both cerebellar lobes. A specimen was taken for biopsy, and a decompression was left. The dura was left open, and a catheter was placed in the left lateral ventricle. The catheter was removed five days after operation, but spinal fluid continued to drain from the site. After transient improvement, athetoid movements of all the patient's extremities again developed; these became progressively worse until his death twenty-one days after operation.



FIG. 10. *Superior aspect of the cerebellum, case 3, showing diffuse infiltration of arachnoid with tumor.*

Necropsy was limited to the head. The dura, cerebral arteries, and venous sinuses were normal. The arachnoid over the entire cerebellum, the pons, the medulla, the base of the brain, the lateral surfaces of the cerebrum, and the vertex of the right cerebrum was found to be diffusely thickened by pinkish-gray, homogeneous, neoplastic tissue (Figs. 9, 10). It measured up to 1 cm. in thickness and filled most of the sulci so that the convolutions were somewhat obscured. Between the frontal lobes, there was a mass of similar tissue about 3 by 3 by 4 cm. that merged imperceptibly with the adjacent cortex (Fig. 11). The tumor in the sylvian fissure also infiltrated



FIG. 11. *Horizontal section of the brain in case 3 showing the tumor between the frontal lobes and in the sylvian fissures. It can be seen that the tumor has invaded the cortex. Hydrocephalus is present.*

the cortex slightly. The arachnoid along all the cranial nerves was similarly thickened, and the gasserian ganglions particularly appeared to be infiltrated with tumor. Marked hydrocephalus of the lateral and third ventricles was present (Fig. 11). The tumor extended into the fourth ventricle with the formation of a small nodular mass.

Microscopic examination showed the tumor to be composed of small cells with little cytoplasm. The nuclei were round

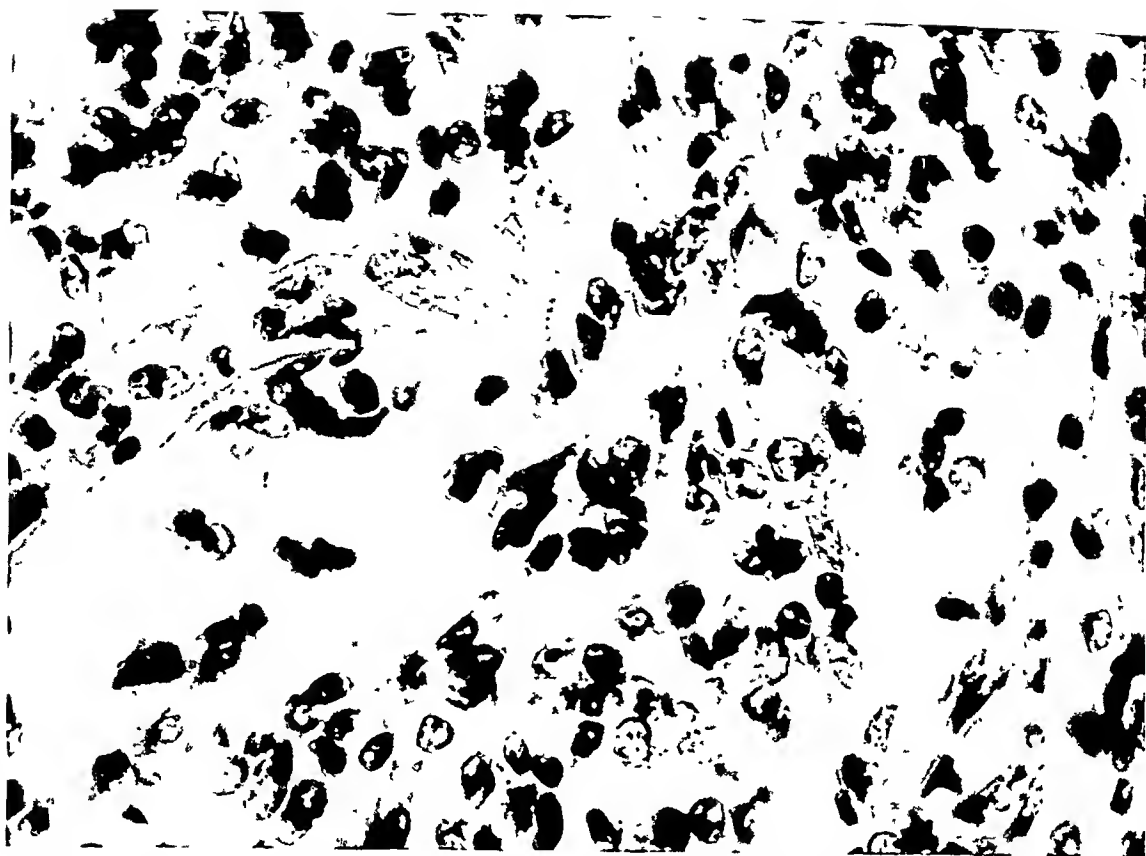


FIG. 12. Tumor in case 3 showing the fibroblastic characteristics of the cells. Note the mitotic figures. (H. & E. $\times 1100$.) This should be compared with Fig. 1.

to oval and in some places they were spindle-shaped. The chromatin was dispersed evenly through the nucleus, and only an occasional nucleolus could be defined. Many of the nuclei were pyknotic, and mitotic figures were abundant. There was considerable pleomorphism, and both giant nuclei and giant cells with multiple nuclei were seen (Fig. 12). The neoplastic cells were divided into small masses by thin strands of connective tissue, and centers of masses of cells were undergoing necrosis in some places. There was an abundant network of reticulin in the areas of viable tissue. The neoplastic tissue invaded the brain in many areas, but it was evident that it did not arise in the parenchyma (Fig. 13). A faint outline of the cortex could still be discerned with the tumor penetrating it in long finger-like processes, mostly along the course of blood vessels. The strands of tumor coalesced to form larger masses. Although the diffuse tumor was confined primarily to the subarachnoid space, in almost every place in which it formed a sizable mass, the parenchyma was invaded in a similar manner. The tumor seemed to

invade particularly the substance of the cranial nerves.

Even though necropsy in this case was confined to the head, we felt that, since there was complete absence of symptoms from elsewhere in the body and particularly since there was no evidence of the few tumors that ordinarily occur in this age group, it was reasonable to assume that this tumor was primary in the meninges. The points in differential diagnosis that excluded medulloblastoma are as follows: 1. Although the tumor had infiltrated the brain in several areas, it was obvious that the tumor had not originated there. 2. The presence of numerous bizarre mitotic figures, the pleomorphism of the cells, and the invasion of the brain made the diagnosis of cancer mandatory. The pleomorphism and the size of the cells in this case (Fig. 12) should be contrasted with these characteristics in case 1 (Fig. 1). 3. The analogy of



FIG. 13. Tumor between the frontal lobes in case 3, showing invasion of the cortex, which, in most places, can still be identified.

these diffuse meningeal tumors originating from connective tissue with solitary tumors arising from the fibrous tissue of the meninges was evident. Four diffuse meningeal tumors that appeared to have both stromal and fibrous components have been found in the literature.^{2, 24, 25} The case of Weinberger was one of a diffuse tumor that involved large areas on the surface of the brain. It showed an intermingling of large vesicular cells and spindle-shaped cells. Mitotic figures and parenchymal invasion were not present, and there was little evidence of pleomorphism. It seemed that this case was the counterpart of the mixed type of benign solitary meningioma. The case reported by Arlt was similar. The case of Hsü and that of Uihlein and associates illustrate how this type may have malignant characteristics. We wish to present the gross and microscopic findings of the latter case in considerable detail for comparative purposes.

Case 4. The clinical history of this boy, 2½ years of age, is presented elsewhere.²⁴ The essential findings were limited to the brain and spinal cord. Grossly, the dura was tense and adherent to the skull in the occipital region around the foramen magnum, where there were multiple soft, deep-red, pedunculated tumors. A flesh-colored, soft,

pedunculated mass surrounded the auditory and facial nerves bilaterally in the region of the petrous bones. Another soft, flesh-colored, pedunculated mass was noted in the posterior clinoid region extending to the anterior border of the foramen magnum. The cerebral arteries and venous sinuses were normal. The arachnoid over the brain and cerebellum was thin, delicate, and translucent except for multiple, small, pedunculated tumors over the lobes of both cerebral hemispheres. Section of the brain disclosed small, fleshy, pink tumors in the choroid plexuses of both anterior and posterior horns of the lateral ventricles, and the fourth ventricle was almost completely filled with one. The ventricular system was slightly dilated. A pink, friable mass, 5 mm. in diameter, was present in the posterior limit of the right thalamus, and tumor was found in the ventral portion of the pons and medulla. The arachnoid throughout the entire length of the spinal cord and the filum terminale contained neoplastic growth, which was irregularly distributed. It involved particularly the dorsal surface of the spinal cord, where it formed large masses that invaded the cord and replaced large areas of it (Figs. 14, 15). In the lumbar region, the cord was extensively compressed and infiltrated so that nothing remained but the posterior horns of gray matter and

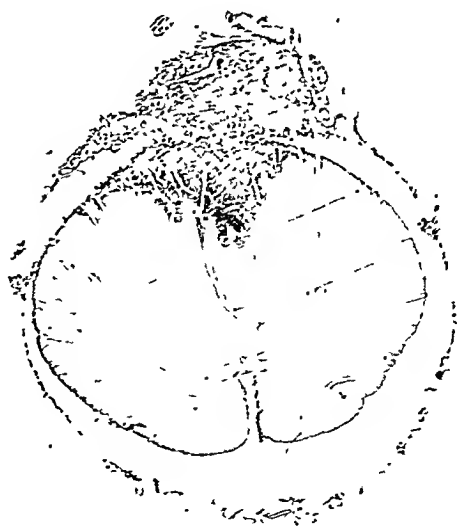


FIG. 14. Diffuse tumor of arachnoid and of thoracic cord, case 4, showing the formation of a large mass. Note invasion of the cord. (H. & E. $\times 8.15$.)

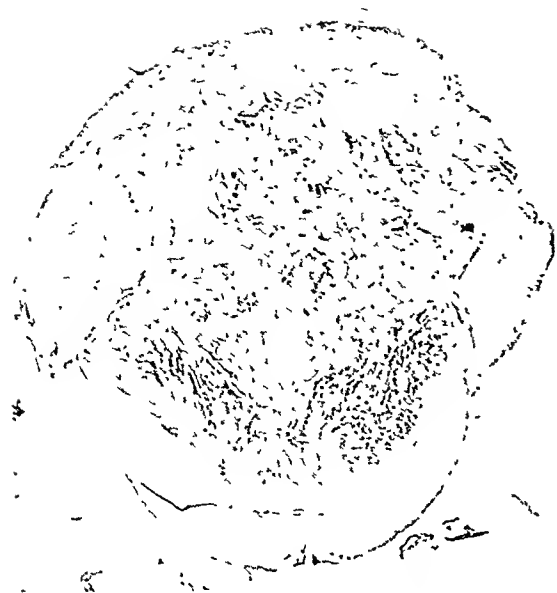


FIG. 15. *Lumbar cord, showing tumor with extensive invasion of cord substance.*

the posterior fasciculi. The filum terminale was a solid tumor.

Microscopic examination of the tumor revealed, in some places, an intermingling of two types of cells. The dural masses showed medium-sized, neoplastic cells divided into small groups by thick strands of loose, fibrous connective tissue. Toward the periphery of the masses, the connective tissue was less abundant and the strands were narrower. The cells within the collagenous tissue were oval, plump, and light-staining, as contrasted with the long, narrow, dark-staining fibrocytes usually seen in connective tissue. This intermingling of cells was seen in several tumors from areas away from the dura, so it appeared that the fibrous tissue did not represent merely a reaction of the dura to the tumor but an integral part of it (Fig. 16). Most of the neoplastic cells of apparent arachnoid origin had no obvious cytoplasm, and the others had only a tiny rim of it. The nuclei varied from round to oval, but considerable pleomorphism was present. The chromatin was unevenly dispersed in fine strands, giving a somewhat vacuolated appearance to many of the cells. Many nuclei were present, which were stained so intensely that detail was obscured. Mitotic figures were numerous, and bizarre mitotic figures were easily found (Fig. 17). A heavy reticulum in intimate relation to the neoplastic cells was present. Invasion of the parenchyma, noted grossly, was confirmed microscopically. In addition, tiny collections of

neoplastic cells were found in the subarachnoid space in areas where a tumor had not been detected grossly.

The masses that occurred in the dura in association with a diffuse meningeal tumor were a unique finding but one that would be expected in the light of the pathogenesis of meningiomas apparently arising in the dura. If large areas of meningeal tissues were transformed into tumor and a portion of that tissue, that is, pacchionian granulations, was normally within the dura, it is to be expected that it would undergo neoplastic transformation. The rapidity of growth and the malignancy of the tumor obscure the dual nature of this neoplasm in most areas; however, portions of the tumor not associated with the dura show a large amount of connective tissue, the characteristics of which strongly indicate a neoplastic nature.

ORIGIN OF PRIMARY DIFFUSE MENINGEAL TUMORS

Weinberger, who based his conclusions largely on the work of Globus, explained the origin of primary diffuse meningeal tumors as well as the differences in the lesions on the basis of abnormal fetal development. He stated that the mesenchymal endomeninx, which normally forms the pia and arachnoid, may persist in certain instances into postnatal life. This malformed or unformed layer may give rise to diffuse sheetlike tumors in which neither the pia nor the arachnoid may be identified, but which contain elements of both. This group he termed "diffuse leptomeningeal type of meningiomatosis." He assumed that partial differentiation as well as partial arrest of endomeningeal development may occur with the survival into postnatal life of an undifferentiated and primitive arachnoid in association with a normally formed pia or vice versa, termed respectively "diffuse arachnoidal type" and "diffuse pial type" of meningiomatosis.

Even though many older pathologists subscribed to the embryological origin of

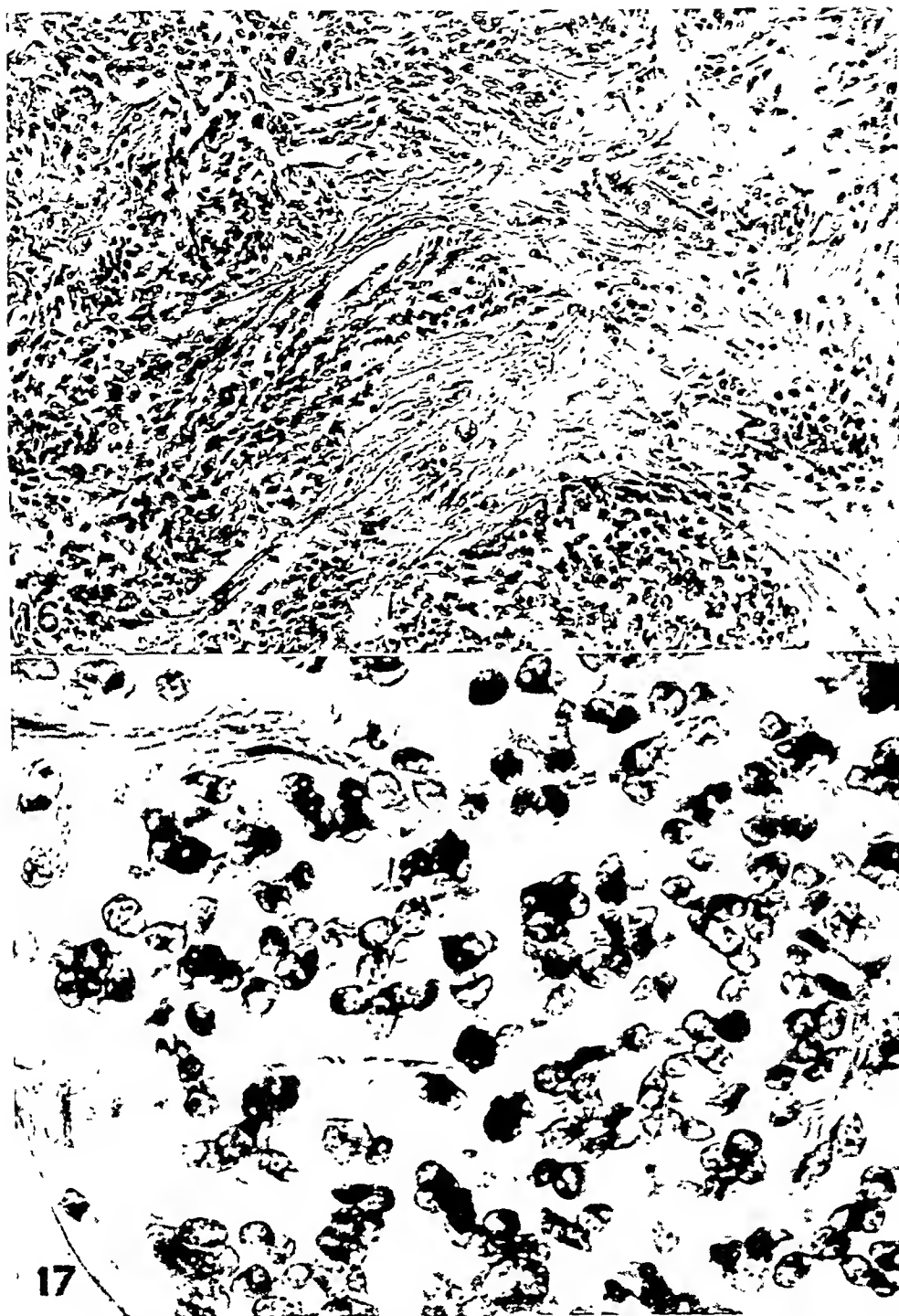


FIG. 16. Tumor from the center of a mass entirely separate from the dura in case 4. The cells of the stroma also have neoplastic characteristics. (H. & E. $\times 187$.)

FIG. 17. Characteristics of the tumor cells in case 4 are shown. (H. & E. $\times 950$.) These should be compared with Figs. 1, 9, and 16. Note the numerous mitotic figures.

tumors, this idea has been discarded by most modern students of neoplasia, except in relation to some specific tumors such as nephroblastoma and retinoblastoma. Willis stated, concerning this, "Indeed the germ-layers, the status of which has of recent years greatly declined even for the embryologist, are devoid of significance for the pathologist" and Ewing concluded "The behavior of tumor cells is very much more influenced by the acquired characters of the cells of origin than by their embryological derivation. . . . The neoplastic process does not consist in retracing the steps of embryological development." One may consider these tumors as arising spontaneously in large areas of the arachnoid, without incriminating an embryological background. As has been indicated, the rapidity of growth may vary considerably from tumor to tumor within the group and even in different areas within the same tumor.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is concerned with other diffuse tumors that involve the meninges. These include diffuse tumors of gliomatosis, carcinomatosis, metastatic sarcomatosis, primary and metastatic tumors of melanomatosis, and primary sarcomas, either perivascular or possibly originating in a meningioma, with diffuse meningeal spread. Of the diffuse tumors of gliomatosis, the medulloblastoma is most apt to present difficulties in differential diagnosis. The other gliomas are usually readily differentiated by study of the cytology, aided by Mallory's stain, by means of phosphotungstic acid-hematoxylin and by silver reticulin impregnations. None of these gliomas produce reticulin, and when the reticulin pattern is marked, the stromal cells in the tumor are evident and can be readily distinguished from the neoplastic cells. The differential diagnosis between perivascular sarcoma and the primary meningeal tumors depends fundamentally on the presence of a localized mass in the brain. If a specimen of tumor away from the mass is removed

for biopsy in a case of perivascular sarcoma, the differential diagnosis cannot be made. In metastatic sarcomatosis and carcinomatosis, the primary lesion is usually clinically obvious or is found at necropsy. Carcinomatosis can usually be diagnosed by cytology. In primary melanomatosis and metastatic melanomatosis, the cells can be differentiated from the cells of meningeal meningiomas by demonstrating the melanin pigment, which may be evident only by the dopa reaction or with the use of Becker's silver method.

TERMINOLOGY

Since the discussion concerning the origin of the meninges is still active, it may be well to retain the noncommittal term "meningioma" as the generic term for the entire group of tumors primary in the meninges, with the added connotation of a benign solitary tumor. For the more rapidly growing counterpart that is more apt to recur, the term "malignant meningioma of meningotheial or fibroblastic type" may be used. For the multiple discrete tumors arising from the meninges, the term "multiple meningiomas, meningotheial or fibroblastic type" could be employed. For the diffuse tumors arising from the meninges the following terminology is suggested: benign or malignant diffuse meningiomatosis, of meningotheial, mixed, or fibroblastic type.

SUMMARY

We have presented four cases of diffuse meningeal meningiomatosis. Evidence supports the fact that there are two types of cells in the meninges. In two of our cases, tumors appear to have arisen from meningotheial cells, one from fibroblasts, and one of mixed type from both meningotheial cells and fibroblasts. This suggests that both elements of the meninges may undergo diffuse neoplasia. Our cases were of children or young adults, as have been most cases reported in the literature.

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SOLITARY FIBROUS MESOTHELIOMA OF THE PERITONEUM

ARTHUR PURDY STOUT, M.D.

IN 1942, the writer in collaboration with Murray published a case report of a malignant pleural tumor that we elected to call a mesothelioma because, when explanted in vitro, the tumor cells displayed the characteristics of mesothelium. The tumor did not have the classical appearance of the diffuse mesotheliomas but was composed of spindle-shaped cells, was supplied with many reticulin fibers between the cells, and was quite vascular. Since that time, sixteen cases of solitary mesothelioma of the pleura have come to my attention, and eight of these that are well documented have been included in a paper by the writer and Himadi.⁵

These pleural tumors manifest themselves both in benign and malignant guise. The benign growths are sharply circumscribed, project outward into the pleural cavity, and are either pedunculated or indent the lung or tissues of the chest wall. They grow slowly and may reach a very large size before being discovered. The malignant tumors are also circumscribed but are not pedunculated, and although they have a broad attachment to the pleura, are buried in the substance of the lung or chest wall. They are grossly circumscribed but actually infiltrate. Microscopically, the benign tumors have a characteristic appearance that is easy to recognize but hard to describe because in each case it is so varied. The type cell is spindle-shaped and imitates the appearance of a fibroblast. A great many thick and thin connective-tissue fibers are formed, but the number and thickness of these vary absolutely in all parts of the growth in such a fashion that it is impossible to select any one field as characteristic. Moreover, the growth varies absolutely in degree of

vascularity and in viability in different areas, hence, one may expect to find no uniformity of these features. The spindle-shaped cells always have a differentiated aspect, so that no matter how bizarre their arrangement, the individual units taken by themselves do not impress one as anaplastic or malignant, as indeed they are not.

The malignant tumors are much more cellular, with fewer reticulin, and no collagen, fibers. There is variability in the degree of vascularity and degree of necrosis in different areas of the same tumor, and it is this variability chiefly that distinguishes the tumor from the fibrosarcomas and leiomyosarcomas with which it could be most easily confused.

The benign and malignant varieties of these pleural tumors have been repeatedly reported but almost always under different names such as fibroma, fibrosarcoma, fibrosarcoma myxomatodes, myxosarcoma, leiomyosarcoma, sarcoma, sarcoma-like tumor, giant sarcoma of the pleura, endothelioma, and endothelial sarcoma. No one author apparently saw more than two or three of the cases, and therefore it never occurred to any of them that this galaxy of names actually had been used to describe a single variety of neoplasm. The writer had the advantage of studying a considerable number of these tumors together, which convinced him that they formed a single class that differed in its bizarre histological aspects from any tumors in other parts of the body with which he was acquainted. There was also the fortunate observation of Murray on one of them that grew mesothelial cells in an explant. Dr. Murray's interpretation persuaded him that the whole group could be regarded as mesothelial derivatives and as examples of the versatility of the mesothelial cell, which Maximow had shown, as long ago as 1927, was capable of acting as a

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Received for publication, April 17, 1950.

fibroblast when explanted in vitro. The term "mesothelioma of the pleura," which was used by Stout and Murray in 1942, was therefore retained in the more recent paper by Stout and Himadi. The descriptive adjective "localized," while accurate, did not seem quite so arresting as "solitary" and was therefore subordinated to the latter.

These observations were very satisfactory as far as the pleural tumors were concerned, but the writer felt it was very peculiar that no similar tumors had been described as arising from the other mesothelial membranes, namely, the pericardium and peritoneum. It was therefore with a sense of lively satisfaction that he came across the case reported herewith, which exactly resembles the benign pleural mesotheliomas not only in its clinical characteristics but in its gross and microscopic appearance.

CASE REPORT

History. F. C., a 68-year-old American man of Italian parentage, was apparently perfectly well until two or three months before admission to the Presbyterian Hospital, April 4, 1947, when, without known cause, he began to lose weight. His appetite was good until one week before admission. At that time, his family noticed that he had become disoriented and his speech slurred. His condition deteriorated rapidly, and three days before admission he was found collapsed in the bathroom. When admitted, he was unresponsive and no satisfactory explanation of his condition was found.

The hemogram was normal; the erythrocyte sedimentation rate, 21 mm. per hour; Kline reaction, negative; urea nitrogen, 9 mg.; serum amylase, 35 units (Myers and Killian). The urine showed a trace of albumin. The stool was guaiac negative. The spinal fluid showed proteins, 46 mg.; sugar, 57 mg.

The abdomen was protuberant, and a large firm mass was palpated in the right upper quadrant and epigastrium. It moved with respiration and did not pulsate. A roentgenogram of the chest showed a shadow in the right lower lung field suggesting calcification of the pleura and a little calcification of the pleura at the left apex. Otherwise the lung fields were clear. There was some calcification of the aortic knob.

The patient improved with rest in bed



FIG. 1. Photograph of the tumor, showing the serosal covered, knobby surface.

and became clearer mentally. It was suspected he had a cancer and exploration to find out was determined upon.

Operation. This was carried out by R. G. Schullinger on May 26, 1947. The mass proved to be a large, roughly ovate, encapsulated tumor about the size of a large grapefruit. It was rubbery and its surface nodular. There were many large vessels in the capsule. It seemed to arise just mesial and inferior to the proximal duodenum but without connection to it or to the pancreas. The tumor pushed forward between the distal portion of the greater curvature of the stomach and the transverse colon, thus stretching and pushing forward the gastocolic omentum. After dividing the gastocolic omentum, the tumor was easily freed; its attachment to the retroperitoneum cut after its nutrient vessels were clamped, cut, and transfixed; and the entire tumor removed intact.

The patient made an excellent recovery and left the hospital June 5, 1947, ten days after operation. His physician, Terence L. Tyson, reports, April 13, 1950, that there is no evidence of recurrence nearly three years after operation.

Gross Specimen. The resected mass measured 14×16×9 cm. and weighed 1168 gm. The surface was covered with peritoneum containing large veins except at the clamped pedicle. Several knobs projected from the surface. When bisected, it was solid and of a yellowish-gray color. The tumor tissue



FIG. 2. The tumor bisected, showing the variations of density and degree of preservation.

was fibrous but friable, with areas of cleavage representing degeneration. In some areas, there were quite large vessels within the tumor. One of the projecting knobs was hard, fibrous, and partly calcified.

The tumor was fixed in Bouin solution, alcohol, formalin, chloralhydrate, and Zenker's fluid. Tissues were stained in hematoxylin and eosin, Masson's trichrome stain, impregnated by the Cajal method, stained for glycogen, and with Scharlach R. (Figs. 1, 2).

Microscopic Description. The dominant cell in this tumor had a spindle shape, with a correspondingly elongated nucleus devoid of large nucleoli and showing only occasional mitoses. The cell cytoplasm, best seen with Masson's trichrome stain, contained no fibrils or granules. The cytoplasm was faintly acidophilic and tended to appear in discontinuous masses of nondescript aspect. These cells were accompanied by connective-tissue fibers of varying thickness. In places, these had contracted so that cells and fibers appeared to run in wavy bands. Unlike the majority of spindle-cell tumors and fibroblastic ones in particular, these bands of

cells and fibers did not interlace or form any other definite pattern but ran vaguely and at haphazard, so that they did not appear to have any definite beginning or end. The picture was further confused by the marked variations in the thickness of the fibers that sometimes dominated the picture to the exclusion of almost all cells and elsewhere, often close by, almost completely faded out of the picture. These areas sometimes were distinguished by focal degeneration, hemorrhage, or both. Blood vessels were equally capricious in frequency and size. Thus the impression was gained of a fibrous growth the characteristics of which were its complete lack of any definite growth pattern and its variability. These features are so striking as to make it easily recognizable once it has been seen. The various special techniques employed all gave negative results. No axis cylinders were found in the Cajal impregnations, almost no glycogen was present, and the only lipoid was in degenerate cells. (Figs. 3, 4, 5, 6.)

DISCUSSION

The primary tumors of the mesothelium of the pleura, pericardium, and peritoneum

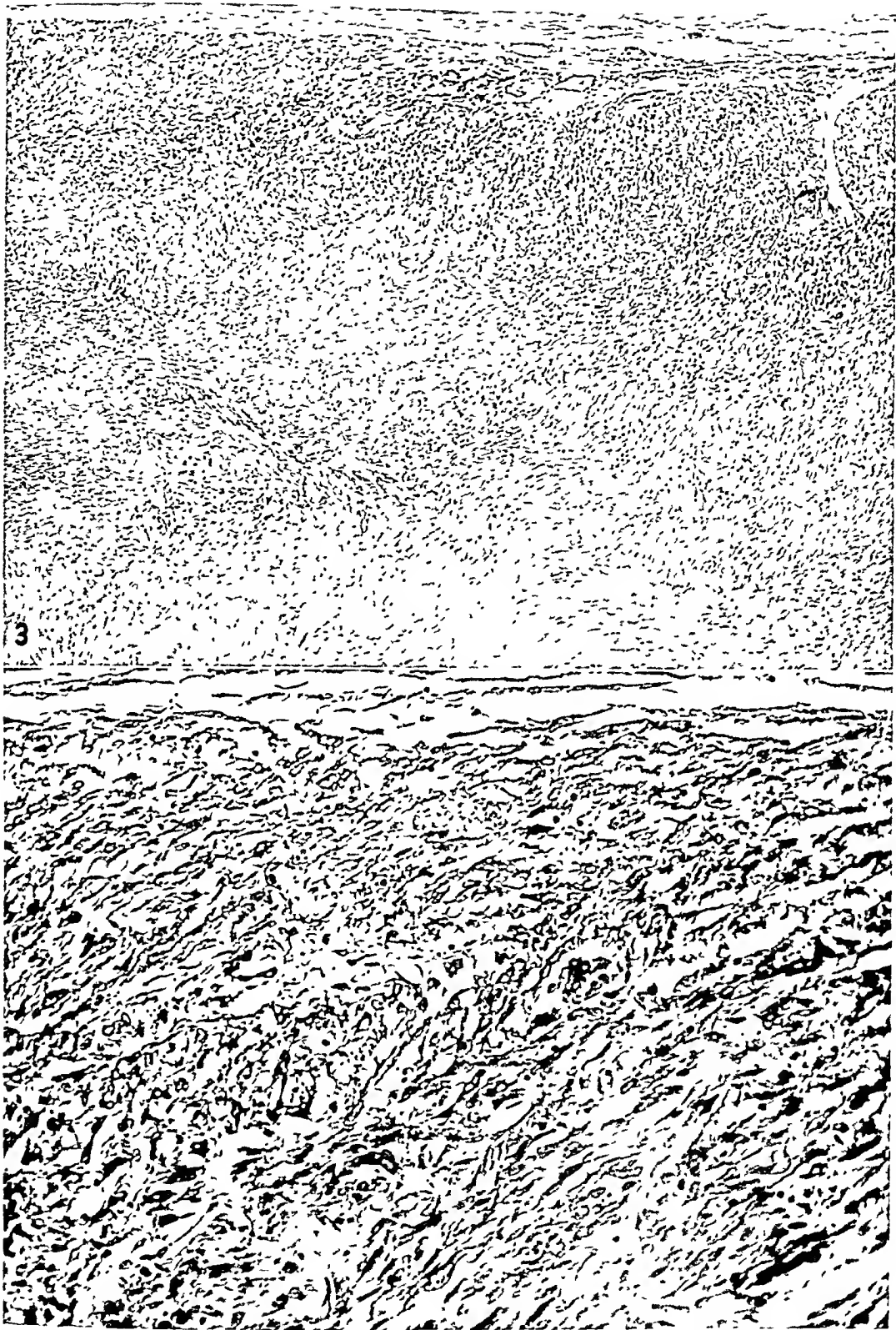


FIG. 3. Section of the tumor through the capsule. Just beneath it, the tumor is well-preserved. At the bottom, the growth is so densely fibrous that few nuclei are present. ($\times 36$.)

FIG. 4. Detail of Figure 3, showing spindle-shaped cells and connective-tissue fibers in irregular arrangement beneath the capsule. The larger collagen fibers near the bottom of the picture have contracted and course in sinuous waves. ($\times 225$.)

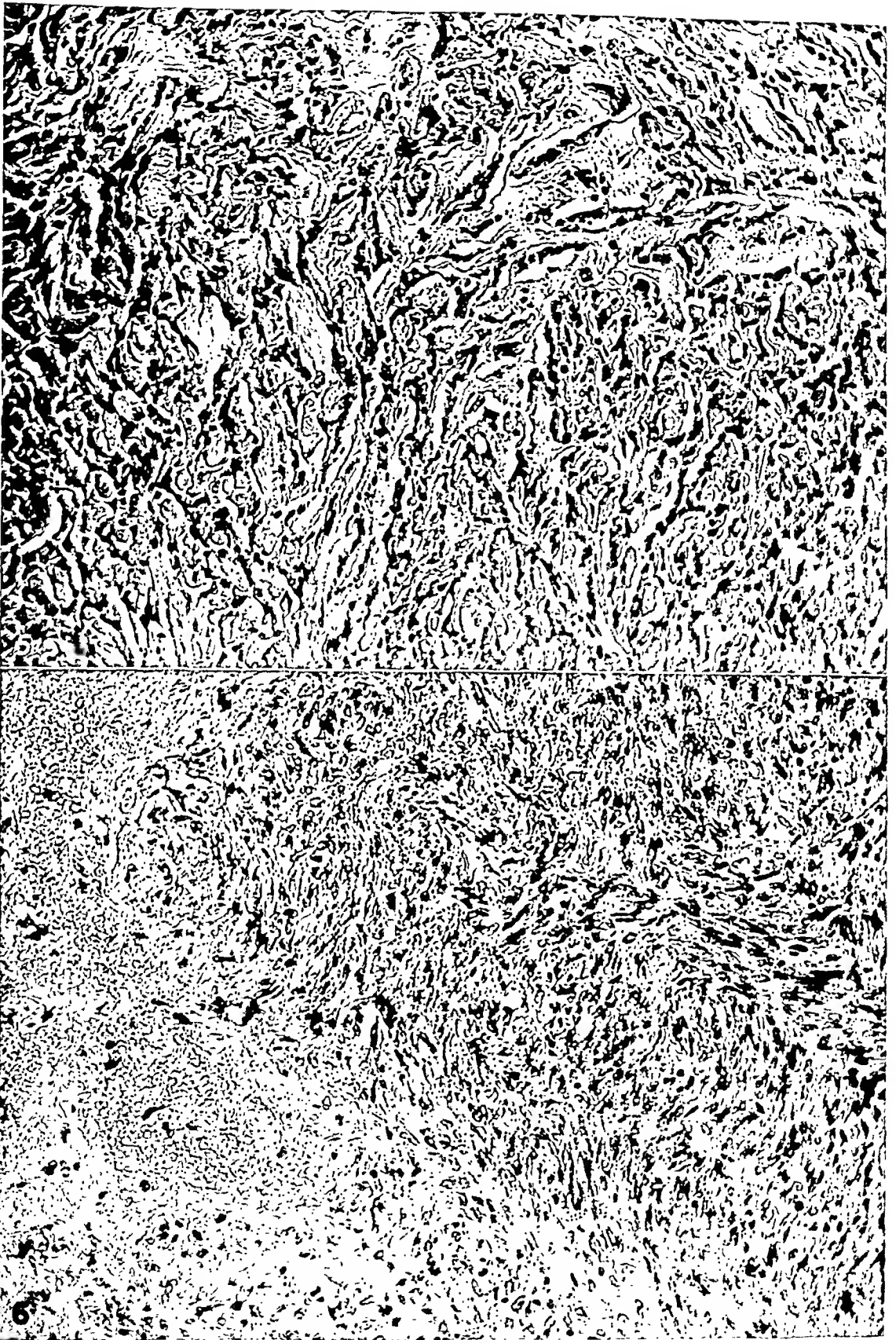


FIG. 5. Detail from an area in the tumor where the collagen fibers are thick and prominent and the tumor cells small and inconspicuous. ($\times 225$.)

FIG. 6. Detail from an area in the tumor where there is a focus of hemorrhage and necrosis. ($\times 225$.)

are quite confusing because of the different aspects that they may assume. Three different varieties have been described:

1. *The diffuse, spreading, malignant growths* that are characterized by the formation of tubes lined by swollen anaplastic mesothelial cells that secrete hyaluronic acid. These tumors spread widely and thicken the pleura or peritoneum without deep penetration and almost never metastasize. They are rare tumors and since metastatic carcinoma can sometimes behave in the same fashion, probably not all tumors reported as diffuse mesotheliomas are such. They are more common in the peritoneum than in the pleura or pericardium. In the Laboratory of Surgical Pathology of Columbia University, there are sixteen in the peritoneum, whereas only two cases have been recorded in the pleura and two in the pericardium. The existence of this tumor and its origin from mesothelial cells is recognized by almost everyone.

2. *The benign mesotheliomas of the male and female genital tracts.* These are small nodules composed of tubules lined by cells that secrete a mucoid substance. They have been observed in the epididymis, cord, round ligament, uterine tube, canal of Nuck, and serosal surface of the uterus. They have not been described in the upper part of the peritoneal membrane, nor in the pleura or pericardium. The writer agrees with Masson, Riopelle, and Simard, and with Evans, that they are benign mesothelial neoplasms; but there are many who disagree, notably Golden and Ash who call them adenomatoid tumors, and others who have suggested that they are real adenomas, adenomyomas, or lymphangiomas.

3. *The benign and malignant solitary fibrous mesotheliomas* that heretofore have been recorded only in the pleura. With the present case, the possibility of their occurrence in the peritoneum has been shown.

The opinion here expressed, that these last should be considered as tumors derived from mesothelial cells and therefore deserve the name mesothelioma, no doubt will en-

counter resistance because they differ so markedly from the generally accepted conception of a mesothelial tumor. The writer realizes that the basis for this hypothesis does not rest upon a solid scientific foundation, for it has not been possible to culture any of the other tumors to see if they would show the same characteristics in vitro as were demonstrated by the cells of the only case explanted. He does feel convinced that, whatever the cellular origin, these tumors form a coherent group and deserve to be called by the same name, so that they may be recognized when encountered, and larger numbers of them collected for the purpose of learning more about their characteristics and behavior.

SUMMARY

A tumor of the peritoneum has been described that exactly resembles similar tumors in the pleura called originally, by Stout and Murray, localized mesotheliomas, and by Stout and Himadi, solitary (localized) mesotheliomas. It is an example of the benign variant of that group of tumors and is an encapsulated fibrous tumor differing in its growth pattern from all other fibrous tumors in regions other than the mesothelial membranes. Since it differs markedly from the benign tumors called mesothelioma by Masson, Riopelle, and Simard, and by Evans, it seems wise to add the adjective fibrous to its name in order more specifically to identify it.

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EMBRYONAL RHABDOMYOSARCOMA OF THE HEAD AND NECK IN CHILDREN AND ADOLESCENTS

G. DORR STOBBE, M.D.,^{*} and HAROLD W. DARGEON, M.D.

SARCOMA botryoides in female infants and its analogue, the sarcoma developing in the vicinity of the bladder base and prostate in male infants, are well known to pathologists and clinicians alike. The pronounced tendency toward the appearance of embryonal striated muscle in these tumors has led to their designation as embryonal rhabdomyosarcoma, although the occurrence of other mesenchymal elements may justify the terms "mixed mesenchymal tumor" or "mesenchymoma." The former of these is probably not to be preferred because of its more recent employment to designate the complex endometrial tumors of the uterus in the adult, tumors different histologically, histogenetically, and behavioristically.

The fact that a similar group of tumors (characteristically containing a large embryonal striated-muscle constituent) occurs in the head-and-neck area in early infancy and up through adolescence appears to be less well known, to judge by the confusion in the diagnoses made on the tumors received by the Children's Tumor Registry. These lesions are confused with neuroblastoma and even with lymphosarcoma. The purpose of this paper is to call attention once more to the existence of this group of embryonal rhabdomyosarcomas arising for the most part in the orbital, facial, and cervical musculature. These tumors, unfortunately, are rarely recognized early in their clinical course, often misdiagnosed pathologically, for the most part lethal in outcome yet not

entirely so, hence offer some hope of cure with earlier and better diagnosis.

Fifteen such cases have appeared in the Memorial Hospital files during the past seventeen and one-half years. Not all were treated in this hospital. In Table 1, the cases and pertinent data are listed.

PATHOLOGY

Gross Morbid Anatomy. The gross appearance of the tumor varies. The tumor arises within muscle and grows by expansion and infiltration. It seems that expansile growth occurs, but in this rapidly growing embryonal type, infiltrative, destructive growth predominates. When tumor is first encountered, the usual size varies from 1 to 3 cm. in greatest dimension, in advanced cases, it may reach almost any proportion. Smaller lesions are oval, spherical, or elongated. If the tumor is in the center of a muscle, for example, an extraocular muscle of the orbit, the involved muscle, which is usually on the nasal side, is distended; if it occurs in the periphery of a muscle, as in the neck, the growth is longitudinal along the intermuscular septa. The slightly elevated cut surface of the tumor may give an appearance suggestive of circumscription or encapsulation but this is an illusion, and tumor, when seen histologically, actually will be found to extend beyond its apparent edge. The color may be white, or pearl-gray and opaque, reddish-pink or red, depending upon the blood content. The tumor may be either firm, rubbery, or soft, since the consistency will vary with the amount of collagen. The presence of poorly demarcated, soft, yellow regions, or cysts, is the result of degeneration or necrosis. In the palate or nasopharynx, the mucosa overlying the tumor is bulging, and usually there is a

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Received for publication, April 17, 1950.

TABLE 1
CASES OF EMBRYONAL RHABDOMYOSARCOMA

Case	Sex	Age	Site	Clinical diag.	Time before treat.	Excision	Other treat.	No. recur.	Irradiation				Metas.	Dead after treat.	Alive with tumor	Alive without tumor	Total surv. time
									X-rays	X-rays	X-rays	Radium					
									prop.	postop.	alone	postop.					
1*	M	22 Mos.	Region, l. parotid	Lymphadenitis Cyst	3 1/2 Mos.	1 partial	Biop. Folie acid	2	—	2	—	1	None	1 Mo.	—	—	1 Yr. 2 mos.
2	F	8 Yrs.	Soft palate	Cystic tumor	3 Mos.	1	Biop.	1	—	3	—	2	Pos.	6 Mos.	—	—	1 Yr. 1 mo.
3	M	6 1/2 Yrs.	R. orbit	Fibrosa.	3 Wks.	—	Biop. Exent. orbit	—	—	1	—	—	None	—	—	12 Yrs. 1 mo.	12 Yrs. 7 mos.
4	F	8 Yrs.	L. tonsil	Tb lymphadenitis Tumor	1 1/2 Mos	1	Biop.	1	1	1	—	1	None	—	12 Mos.	—	12 Mos.
5*	M	2 Yrs.	L. temp. region	Tumor	5 Mos	3	Biop. Exent. orbit. incomp.	1	—	—	—	—	None	2 1/2 Mos.	—	—	2 Yrs. 2 mos.
6*	F	2 Yrs.	L. orbit	Rite	1 Mo	1	Drain. abscess with biop. Exent. orbit	3	—	1	—	1	None	5 Mos.	—	—	3 Yrs. 9 mos.
7*	F	16 Mos.	L. palate	Cyst	2 1/2 Wks.	1	Biop. 2 resect 1 maxilla	2	1	—	—	1	Pos.	3 Wks.	—	—	1 Mos.
8*	F	6 1/2 Yrs	L. mastoid	Otitis media Tumor	5 Mos	—	Biop. 2 mastoid-ect SK 1495	1	—	2	—	—	Pos.	10 Days	—	—	1 Yr. 10 mos.
9	M	16 Yrs.	L. orbit	Tumor. sclera	2 Wks.	—	Exent. orbit L. rad. neck dissect.	—	—	—	—	—	Pos.	—	7 Mos.	—	7 Mos.
10*	M	5 Yrs.	Angle, l. jaw	Mal tumor, bone	1 Mo.	—	Biop.	—	—	—	1	—	Pos.	6 Wks.	—	—	7 Mos.
11	M	2 Yrs. 9 Mos.	L. mastoid, ear drum	Tumor	1 Mo.	—	Biop.	1	—	—	2	—	None	8 Mos.	—	—	11 Mos.
12	F	7 Yrs.	Region, l. inf. canthus	Lymphosa.	3 Wks.	1	Exent. orbit	2	—	1	—	1	None	2 Mos.	—	—	1 Yr.
13	F	9 Yrs.	Soft palate	Tumor	6 Wks.	3	Biop., 3	1	1	—	—	2	None	—	—	11 Yrs. 6 mos.	11 Yrs. 6 mos.
14	M	22 Mos	R. neck	Abscess gland	8 Mos.	—	Biop.	—	—	—	1	—	Pos.	3 Mos.	—	—	1 Yr. 3 mos.
15	F	11 Yrs	Region, r. zygoma	Hemangioma	3 Wks.	—	Biop.	2	—	—	2	—	None	6 Wks.	—	—	1 Yr 6 mos.

* Autopsy performed

poorly defined ulcer with a granular base or a fungating granular mass.

Microscopic Description. The embryonal or immature rhabdomyosarcoma has characteristics that may differ in various regions. The predominant cell is a well-defined, short, spindle cell. The nucleus, rich in chromatin, is elongated, with narrow or pointed ends, and is situated near the middle of the cell. The oxyphilic cytoplasm is homogeneous or granular and sometimes vacuolated. These cells form parallel, or anastomosing, and interlacing bands, at times forming a syncytial pattern. Associated with the spindle cells in various proportions are round cells of various types. One kind has a round, hyperchromatic nucleus about the size of a lymphocyte, surrounded by little or no cytoplasm. Another has an oval, or polygonal, vesicular nucleus surrounded by granular cytoplasm. The third type is variable and usually has a round, pyknotic, dark nucleus surrounded by homogeneous acidophilic cytoplasm. This last cell may assume a rectangular shape with frayed ends. Giant cells are common in adult rhabdomyosarcomas but are rarely encountered in the embryonal type. When seen, they are usually oval or slightly elongated cells with several overlapping, distinct nuclei that have deeply staining, evenly distributed chromatin; the cytoplasm is fibrillar. Another type is a large, oval cell having a large, oval, hyperchromatic nucleus and little granular cytoplasm.

When longitudinal fibrils are present, they are in the spindle-shaped cells. Occasionally, a few cross striations are seen in hemotoxylin-and-eosin or, better, in phosphotungstic acid-hemotoxylin preparations, but such striations are only located after a prolonged search. They appear as fine black lines or dots in a phosphotungstic acid-hemotoxylin preparation. They are not present throughout the length of the fibrils but are located at intervals, and then they may not traverse the width of the cell. In cells without well-defined longitudinal fibrils, there are less well-defined fibrils that

exhibit a finely matted appearance. The cells containing fibrils may be regarded as having attained some maturity. Mitotic figures, atypical as well as normal, appear but are not a notable feature.

The stroma contains collagen in various amounts among the cells, as demonstrated by the trichrome stain. The vascularity of the tumors is scanty and in no way characteristic. Argyrophile fibrils surround bundles of spindle-shaped cells or are interspersed among them.

The main difference between the more mature type and the embryonal is the prominence of cross striations in the mature, and paucity or absence in the more embryonal. Also, more anaplastic spindle cells and round cells are present in the embryonal type. Giant cells are prominent in the mature type, and the cells in general are larger.

CLINICAL MATERIAL

Incidence. Fifteen patients with embryonal rhabdomyosarcoma were seen and/or treated at Memorial Hospital from July, 1931, through December, 1949. The mean age was 6.1 years. The youngest was 16 months; the oldest, 16 years. There were six patients, 0 to 4 years; seven patients, 5 to 9 years; one patient, 10 to 14 years; and one patient, older than 15 years. There were seven boys and eight girls; all were white. In two instances (cases 12 and 15), there was a history of trauma, but the trauma seemed to be the initiating reason for scrutinizing the region of tumor rather than the cause. There was no known history of cancer in the families of these patients for two previous generations.

Site. The site of tumor in the fifteen patients was as follows: orbit and region of internal canthus, four cases; tonsil and soft palate, four; mastoid and internal ear, two; region of parotid, zygoma, temporal, and neck regions, five.

Duration of Disease. The mean interval from the onset of symptoms to time of treatment was three and a half months. The

shortest interval was about two and a half weeks (case 7); the longest was eight months (case 14). The mean survival time from onset of symptoms to death in eleven patients was one year and five months, with extremes of four months (case 7) and three years, nine months (case 6). Of the four living patients, two (cases 3 and 13) have survived without apparent tumor twelve years and seven months, and fourteen years and six months respectively, after onset. These are probable cures. Two patients (cases 4 and 9) are alive with tumor twelve and seven months respectively, after onset.

Clinical Findings. The first complaint of each of the fifteen patients was tumor, irrespective of whether the disease was detected in the region of the eye, nasopharynx, ear, side of face, or neck. Hyperemia and heat were present and there was pain if the tumor involved a nerve. The overlying skin exhibited dilated veins. Depending on the site, pressure caused divergence of an eye, abnormal phonation, dysphagia, cough, aural discharge, and deviation of the jaw. The rapidity of the expansile and infiltrative growth increased the severity of complaints, and ultimately there were manifestations of cerebral involvement. When metastases were present, symptoms relative to the organs involved existed.

The first general symptom observed was a slight elevation of temperature, which was due, in most instances, to secondary infection subsequent to ulceration. Usually there was slight leukocytosis, but the hemoglobin was not altered until late in the disease when there was cachexia.

Spread of Tumor. Extensions and/or metastases of the disease were verified by one or a combination of methods, roentgenography, operation, or autopsy in fifteen patients.

In six patients that were examined postmortem, there was local spread only in three (cases 1, 5, and 6), local spread and metastasis in three (cases 7, 8, and 10). By roentgenographic examination alone, local spread and metastasis were demonstrated in

two (cases 2 and 14); these patients died six and three months, respectively, after treatment. Local spread but no metastasis was shown by roentgenograms in cases 11, 12, and 15, and death ensued eight months, two months, and six weeks, after the last treatment.

In patients who are alive, metastasis to a cervical lymph node associated with secondary involvement of the left parotid (case 9) was located in the surgical specimen after a radical neck dissection. Case 4 is alive with local disease in the left side of the neck. She also has tuberculous lymphadenitis in this same site. Cases 3 and 13 are alive after treatment without apparent disease twelve years and four months, and eleven years and six months, respectively.

Thus, of fifteen cases, there was local spread in eleven patients and also distant metastasis in five of these eleven. Regional metastasis was present in one patient who is alive without local recurrence. Three other patients are living, one with local disease and two without clinical evidence of disease.

Local extension of tumor is exemplified in patients representing cases 1, 5, and 6 that were examined postmortem. In case 1, the embryonal rhabdomyosarcoma in the region of the left parotid extended into the hard and soft palate, destroyed the left antrum and wing of the left sphenoid, and entered the cranial cavity. In case 5, there was tumor in the left temporal muscle with extension into the left anterior and middle cranial fossae accompanied by extensive destruction of bone, optic chiasma, and pituitary, and involvement of the left frontal and temporal lobes. In case 6, the tumor, arising in the left orbit, extended into the left frontal lobe, left nares, and left antrum.

Metastases were demonstrable in six patients (cases 2, 7, 8, 9, 10, and 14). The sites were: lungs, four; pleura, three; mediastinal lymph nodes, three; ovaries, two; vertebral column, two; and peritoneum, pelvis, femurs, kidney, uterus, pancreas, thyroid, and brain, one each. In one instance (case 9),

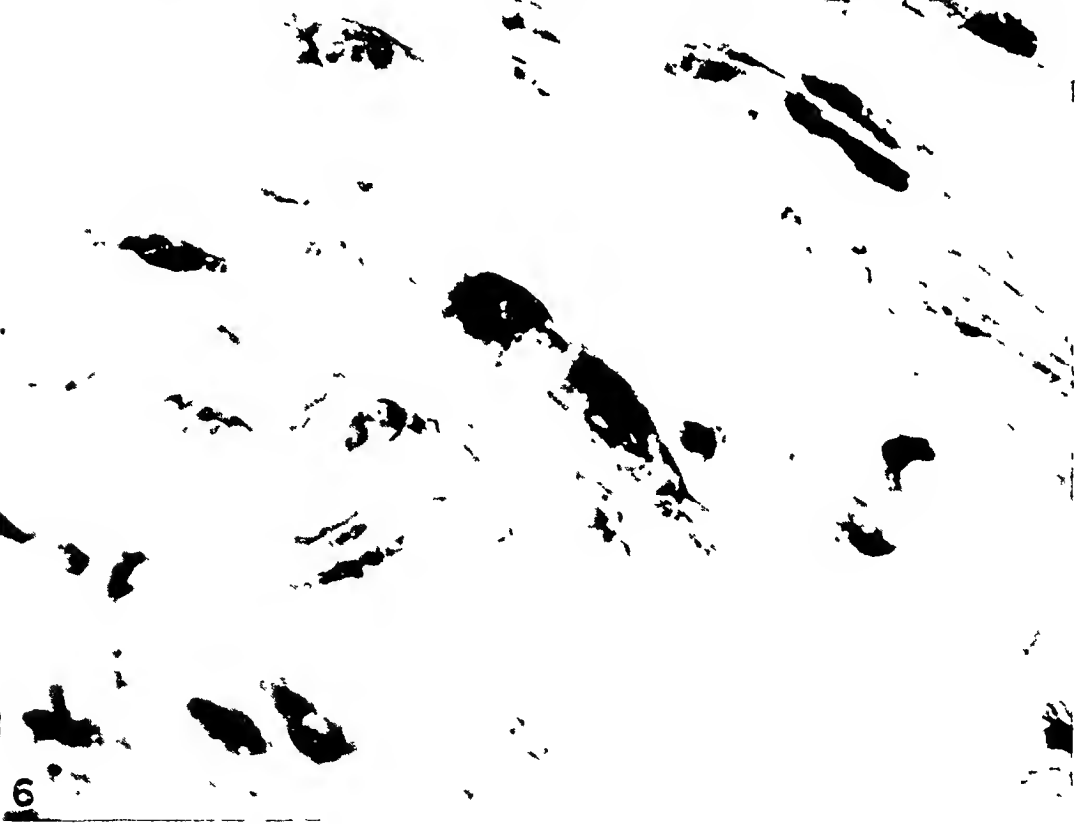
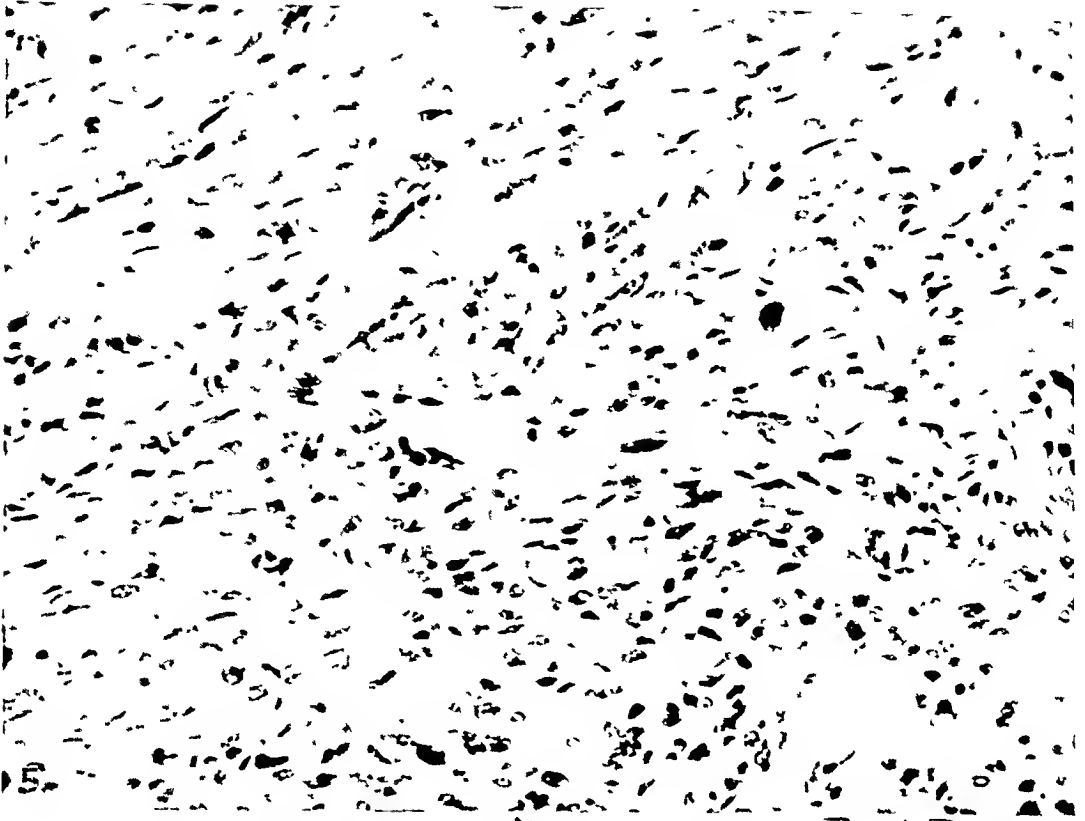


FIG. 5. Case 1. Tumor showing round and spindle cells. (H. & E. $\times 240$.)

FIG. 6. Case 1. Demonstration of cross striations. (Phosphotungstic acid-hematoxylin. $\times 1200$.)



FIG. 7. Case 4. Primary tumor of the left tonsil, after radium and roentgen-ray therapy, showing short spindle cells. (H. & E. $\times 240$.)

FIG. 8. Case 7. Metastatic tumor of lung (autopsy), showing round cells with polygonal, vesicular nuclei and hyperchromatic nuclei. (H. & E. $\times 1100$.)

there was involvement of a regional cervical lymph node and the parotid gland. Thus, distant metastases by both vascular and lymphatic routes were observed. Involvement of regional lymph nodes was rare. The secondary lesions did not differ from the primary. Where regional lymph nodes were palpable, except in case 9, infection, specific or nonspecific, was the pathological finding rather than tumor.

Recurrence. Recurrence of these tumors following local excision, radium, or deep roentgen-ray therapy, is a prominent feature. The tumor is present in the scar and often appears to be in multiple foci. In thirteen of this series of fifteen cases, the tumor recurred from two weeks to one year after treatment. The majority of recurrences were manifested in about three months. The earliest recurrence (case 7) was in two weeks; the latest (case 15) was one year. Because of persistent recurrence and spread of embryonal rhabdomyosarcoma, the prognosis is usually bad. However, undue pessimism is not always warranted. Two children in this series have lived without apparent recurrence for more than eleven years following therapy.

CASE REPORTS

Case 3. A white boy, aged 6½ years, complained of a tender, hyperemic eye, which was treated with boric acid soaks. In one week, the lids were swollen so as to obliterate the palpebral fissure. Following a biopsy three weeks later, an exenteration of the orbit was done and a round mass was found in the nasal side of the orbit. One month postoperatively, deep roentgen-ray therapy was started at Memorial Hospital and continued for seventy days, the total dosage being 9000 r. This patient is apparently free of disease twelve years and four months after the last treatment. The total survival time is twelve years and seven months.

Case 13. A white girl, aged 9 years, had a small tumor in the soft palate above the right tonsil, which was discovered by her mother. About a month later, after biopsy, radium was inserted, and the tumor disappeared within four weeks. After three

weeks, there was a recurrence and radium was used again. There were three more recurrences. Further therapy elsewhere and at Memorial Hospital consisted of two more biopsies, three local excisions, four separate series of treatments with preoperative deep roentgen-ray therapy to the neck and directly over the tumor, and three more trials with radium. The duration of treatment was three years and eight months. The patient is well and free of apparent tumor eleven years and six months after the last radium treatment, and the over-all survival time is fourteen years and six months.

TREATMENT

Different methods and combination of methods have been employed in treatment of this tumor. These are shown in Table I. Surgery alone was used in two patients (cases 5 and 9); deep roentgen-ray therapy alone, in four patients (cases 10, 11, 14, and 15); surgery and postoperative deep roentgen-ray therapy, in two patients (cases 3 and 8). One patient (case 8) also received 2, 6-diaminopurine hydrochloride terminally. Surgery, postoperative deep roentgen-ray therapy, and postoperative radium were employed in four patients (cases 1, 2, 6, and 12). Folic acid was given terminally to one patient (case 1) without effect. Surgery, pre- and postoperative radium, and preoperative deep roentgen-ray therapy were used in one patient (case 13); surgery, preoperative deep roentgen-ray therapy, and postoperative radium in one patient (case 7); surgery, pre- and postoperative deep roentgen-ray therapy, and preoperative radium in one patient (case 4).

It should be noted that the two patients who lived longer than eleven years after the last treatment (cases 3 and 13) were the recipients of radical and aggressive treatment. After biopsy, one patient (case 3) had an exenteration of the right orbit within three weeks of onset of symptoms. One month later, he received deep roentgen-ray therapy (9000 r) to the right orbit over a period of seventy days. The other patient (case 13) had an excision and pathological examination of the tumor in the soft palate within six weeks after discovery of

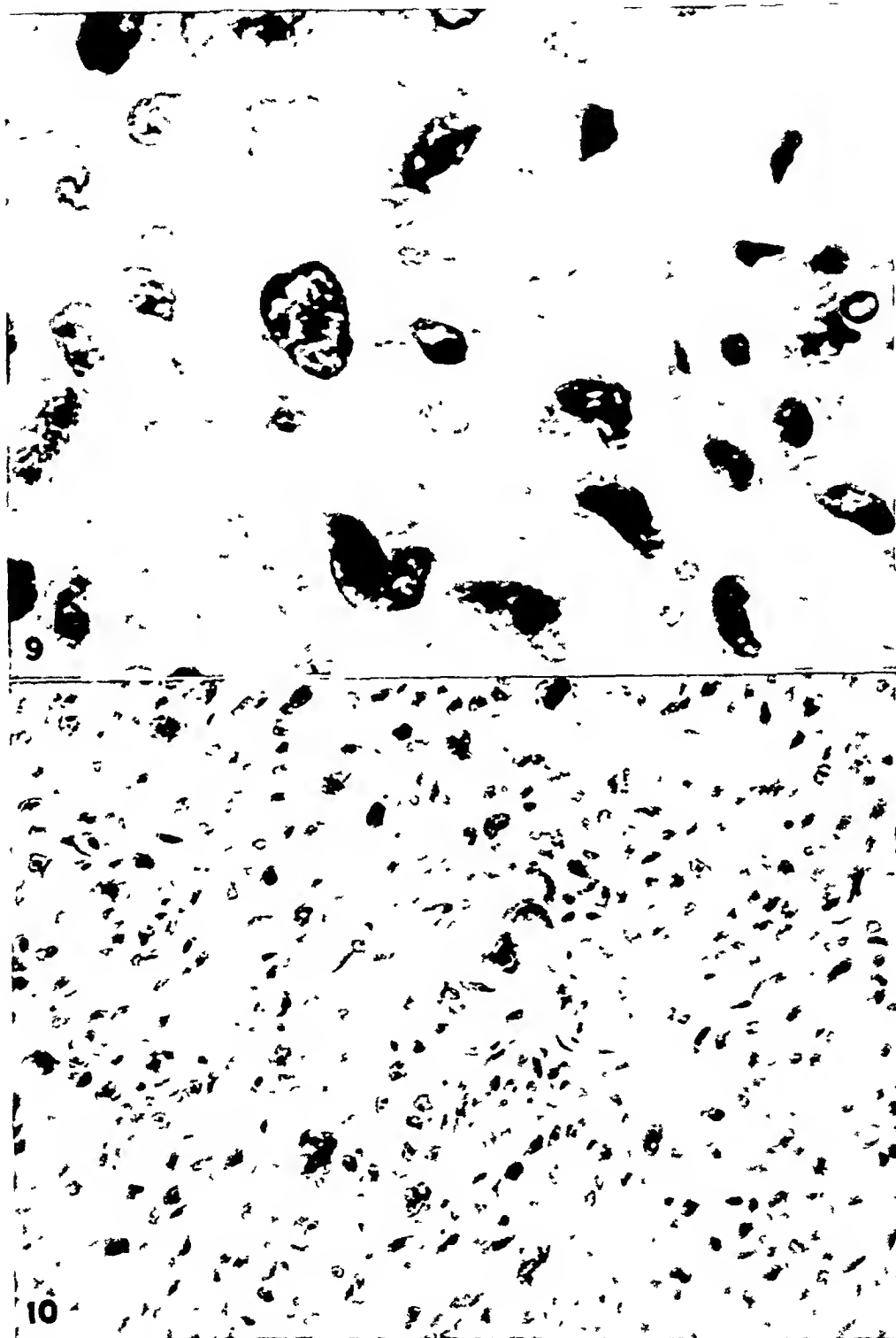


FIG. 9 Case 10 Primary tumor of the angle of left jaw (autopsy), after roentgen-ray therapy. (H. & E. $\times 1100$)

FIG. 10 Case 10. Tumor showing variety of cells. (H. & E. $\times 240$.)

the tumor. Over a period of three years and eight months, she had several more excisions and numerous treatments with radium and roentgen rays, as indicated before. Early in 1948, a basal-cell carcinoma developed in the irradiated area of the left neck. It was biopsied and destroyed by fulguration at another institution.

Wide excision should be the first form of treatment after the diagnosis is proved by biopsy. The margin of clearance should be determined microscopically. In view of the strong tendency to recurrence because of inadequate removal, frequent postoperative examination is necessary. If there is recurrence, excision and postoperative radium or roentgen-ray therapy is mandatory. If there is involvement of regional lymph nodes by tumor, they may be removed providing there is no other metastasis. In view of the fact that the last recurrent lesion in the palate of one patient (case 13) has not recurred in more than eleven years after insertion of radium seeds, it appears that radium and/or deep roentgen-ray therapy is sometimes effective in the treatment of small recurrent lesions.

Treatment has a better chance to effect a cure if the diagnosis is made early. Therefore, periodic examination for tumor is necessary especially in children between the ages of 1 and 6 years, as stated by Rosenblum. Children in this age group do not receive the necessary periodic examinations, except in large communities where nursery schools are in operation. It is during the first five years that the largest number of deaths occur from both leukemia and other cancer.¹ According to Kenney, all tumors in children should be regarded with suspicion, widely excised, and examined pathologically.

SUMMARY

Fifteen cases of embryonal rhabdomyosarcoma in the records of Memorial Hospital during the last seventeen and one-half years were reviewed. The mean age of the patients affected was 6.1 years. The mean survival time in thirteen patients from the onset of the symptoms to death was one year and five months. Two patients are alive and clinically free of disease for more than eleven years after treatment.

The first complaint was tumor. Later, pressure produced symptoms and signs relative to the anatomical site.

The embryonal rhabdomyosarcoma spreads by infiltration and metastasis. The distant metastases are spread via blood and lymph routes. Regional lymph nodes are rarely involved. Microscopically, the predominant cell is a short spindle cell that forms anastomosing and interlacing bands, at times forming a syncytial pattern. Cross striations are found with difficulty. Associated with the spindle cells in various proportions are round cells of several types, and giant cells.

The tumor has a great tendency to recur locally. If treatment is to be effective, it must be done early, and there must be wide excision of the tumor with sacrifice of surrounding healthy tissue. Roentgen-ray and radium therapy are of value as an adjunct to surgery. Periodic examination of children and diagnosis by biopsy of any suspicious lesion are advocated.

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PRIMARY CARCINOMA OF THE LIVER WITH EXTENSIVE SKELETAL METASTASIS AND PANMYELOPHTHISIS

OSCAR AUERBACH, M.D., and SIDNEY TRUBOWITZ, M.D.

ALTHOUGH it is common experience that widespread metastatic involvement of the bone marrow from a primary carcinoma of the prostate, breast, stomach, kidney, thyroid, or other tumor that metastasizes freely to bone can produce a myelophthisis, such sequence of events in the case of a primary hepatoma is extremely rare and, so far as can be ascertained from the literature, has not been reported to date. Hoyne and Kernohan report but thirty-one instances of primary malignant tumor of the liver in 16,903 necropsies, an incidence of 0.19 per cent. Charache, after an extensive review of the literature on primary hepatoma, found but eighteen instances of bone metastases, an incidence of 1.6 per cent of all cases of primary carcinoma of the liver. Because of the unusual and rare occurrence of widespread bone metastases from a primary carcinoma of the liver of sufficient degree to produce a severe panmyelophthisis and hemorrhage, we wish to report the following case.

CASE REPORT

A 49-year-old white man was transferred to Halloran Veterans Administration Hospital from another institution with the tentative diagnosis of acute aleukemic leukemia. The patient's illness apparently began in December, 1946, with a nonproductive cough. Except for a short period of illness in 1942, at which time he was told that he had a "stomach ulcer," the patient

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Sponsored by the Veterans Administration and published with approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect opinion or policy of the Veterans Administration.

Received for publication, March 29, 1950.

had been in excellent health and had worked uninterruptedly for many years as a plumber. When he was first seen by his physician for his cough, he was told that he had "bronchitis" for which aspirin and codeine were prescribed. His cough persisted for about one month and then disappeared. He felt relatively well until February, 1947, when he began to experience severe pain in his back, radiating to both shoulders. In March, 1947, a few teeth were extracted, and procaine hydrochloride was injected on either side of his spine with some relief of pain. However, because of progressive weakness, weight loss, and dyspnea that had come on more or less insidiously, the patient was unable to return to work. His family had noted that he had become quite pale, and it was only on their insistence that he was hospitalized on March 24, 1947.

On admission, the patient was found to be febrile, running a septic type of fever from 101° to 103° F. The back pain disappeared spontaneously, and this complaint was now replaced by severe epistaxis. Roentgenological examination of the chest, lower back, right femur, and left humerus revealed no abnormalities. Further studies, including barium enema, intravenous pyelogram, and a gastrointestinal roentgenographic series were all normal. Routine hematological studies demonstrated the presence of a moderate hypochromic anemia and a slight leukocytosis. The patient was treated with penicillin and blood transfusions, which had little effect on his condition. He became progressively worse, lost 30 pounds of weight, and suffered extreme weakness and dyspnea. On April 4, 1947, he was transferred to Halloran Veterans Administration Hospital.

On admission, the patient was found to be acutely and critically ill. He was very pale, moderately dyspneic, and weak. He was well oriented and highly co-operative. His temperature was 102° F.; pulse, 115; and respirations, twenty-five per minute. All mucous membranes were pale, and there was a slight icteric tint to his sclerae. The nares were filled with dry blood; the tongue

its capsule smooth and glistening. Beneath the capsule were numerous, poorly circumscribed, yellow-white areas. These were firm, rubbery, and varied from 1 mm. to 1.5 cm. in diameter. On cut section, the liver had a cloudy appearance and its color varied from red to green-brown. Within the right lobe of the liver was a sharply circumscribed tumor mass measuring 4.8×3.4 cm. It was gray-white in color and faintly tinged with bile. Contained within the tumor mass were numerous small hemorrhages measuring up to 1 mm. in diameter. The tumor mass surrounded the portal vein and in one area extended deeply into the vessel wall. Distal to this portion of the vessel was a partially adherent clot that filled the lumen of the vessel. Scattered throughout both lobes of the liver were similar, but smaller, gray-white areas.

In the peripancreatic zones, adjacent to the aorta, about the iliac arteries, surrounding the renal arteries, and within the tracheobronchial zones were numerous firm, yellow-brown masses measuring from 1 to 6 cm. in diameter. One of these in the last-named region contained a considerable quantity of dark-red blood clot in its central aspects, while its peripheral portions were composed of yellow-gray tissue similar to that found in the other masses.

The lungs weighed 1956 gm., and contained within them were yellow beadlike nodules along the course of the pulmonary vessels. They measured up to 1 mm. in diameter and extended from the hilus of the lungs to just beneath the pleurae. The peribronchial lymph nodes within the hilar aspects of both lungs measured from 1.5 to 3.5 cm. in diameter and contained soft, poorly circumscribed, yellow areas in their peripheral portions. In addition, the posterior aspects of the lower lobe of the right lung contained numerous raised, firm, red, granular areas measuring from 5 mm. to 1 cm. in diameter.

The heart weighed 482 gm. Apart from the presence of occasional yellow plaques within each coronary artery, which nar-

rowed their lumina, the heart was not grossly diseased.

The spleen weighed 325 gm. The organ was rubbery in consistency, the capsule smooth. Its cut surface was dark red and moist.

Each kidney weighed 295 gm. and showed a red-brown, slightly granular surface. On cut section, the cortical striae were prominent. Just beneath the calyces of each kidney were several petechial hemorrhages.

The cortical zones of the adrenals were golden yellow in color, the medulla brown and mushy.

The prostate measured $4.5 \times 3.2 \times 3$ cm. and contained occasional sharply circumscribed, elevated, yellow-white nodules.

The testes, epididymides, and seminal vesicles showed no evidence of gross pathological change.

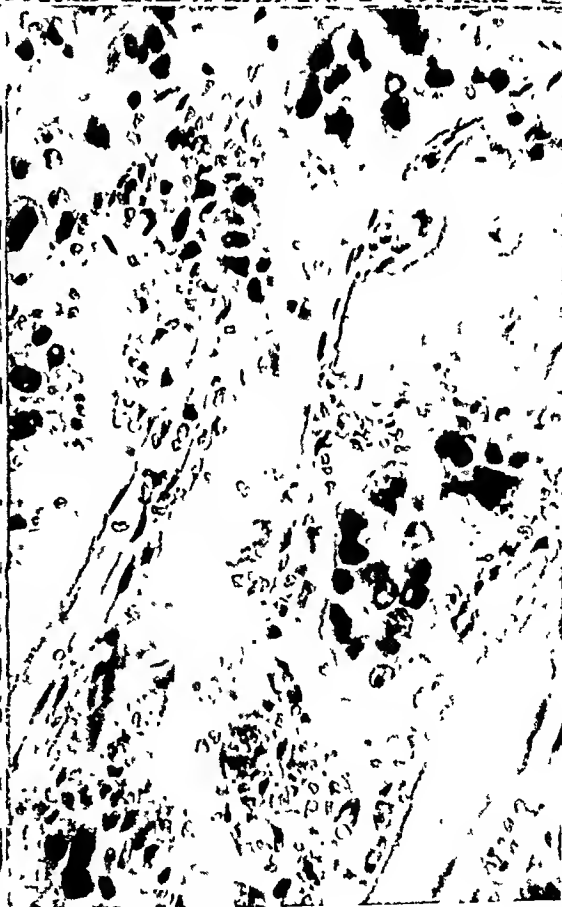
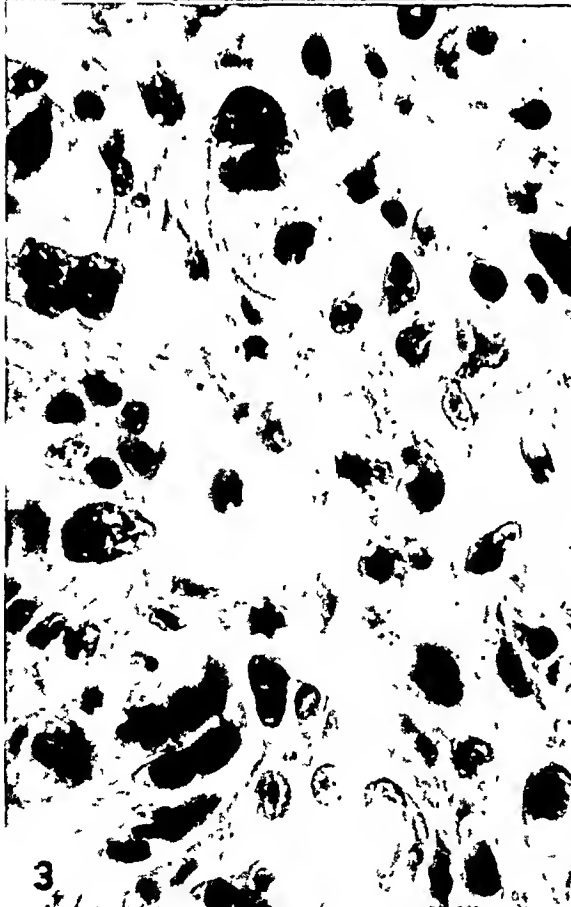
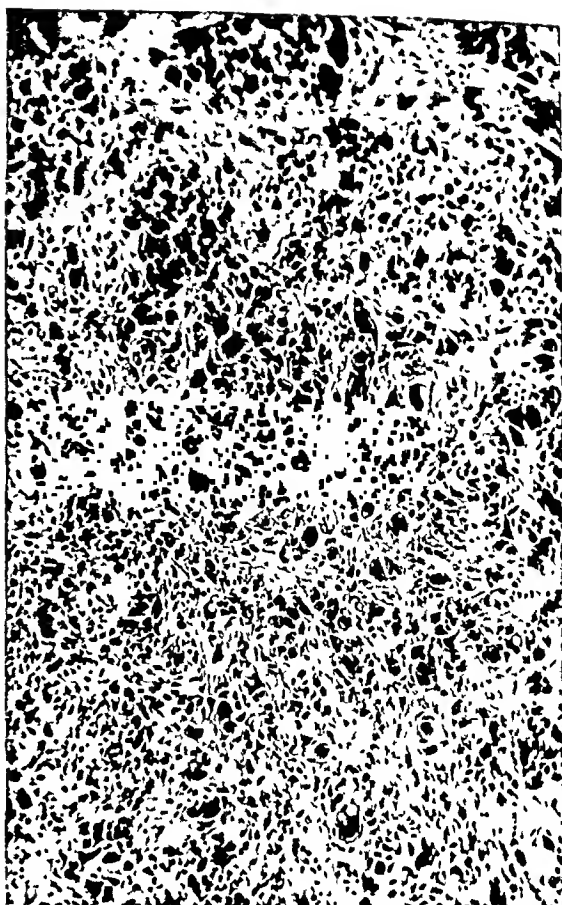
The stomach contained approximately 200 cc. of blood-tinged fluid. The jejunum, ileum, and colon were filled with black, tarry material.

The pancreas was firm and, on section, contained numerous small collections of blood measuring up to 5 mm. in diameter. Within the pancreas were numerous small, sharply circumscribed, yellow-gray areas measuring from 1 to 3 mm. in diameter.

The thyroid gland showed no gross evidence of disease.

The brain weighed 1021 gm. The dura was gray-brown in color, and the dural sinuses contained no gross thrombi. The subarachnoid space contained approximately 200 cc. of fresh blood within it. The superior brain surface was covered with copious amounts of fresh blood. In the posterosuperior aspects of the left parietal lobe, a dark-red, sharply circumscribed area measuring $5 \times 3 \times 2$ mm. separated the meninges from the underlying cortex.

SKELETAL SYSTEM. The marrow cavity of the manubrium sterni contained several light-yellow, sharply circumscribed areas measuring up to 6 mm. in diameter. These yellow areas occupied approximately one



3

(For captions see opposite page.)

third of the available marrow. The remaining portions were dark red in color.

The body of the third lumbar vertebra was narrowed adjacent to one of the periaortic masses already described. On section, the cancellous portions of the third lumbar vertebra had a yellow appearance and contained well-defined, dark-red areas measuring from 5 to 7 mm. in diameter. The marrow spaces of the remaining vertebrae had a mottled pink-gray to dark-red appearance. The cancellous portions of the ribs were uniformly dark wine-red in appearance.

Microscopic Examination. The liver was almost completely occupied by groups of irregular, interlacing tumor-cell cords. These cells were very pleomorphic and had a granular, faintly eosinophilic cytoplasm. Some contained yellow-green material (bile) within them. The nuclei for the most part were clumped, vesicular, and round or oval in shape. Nucleoli, mitotic figures, and tumor giant cells were both numerous and prominent. There was a myxomatous and vascular connective-tissue stroma between the cords of tumor cells, and within it were numerous polymorphonuclear leukocytes, fibroblasts, and collagen fibrils. In some regions, both cell cords and stroma had a pink, granular appearance (necrosis). Such nuclei as remained, within these latter zones, were pyknotic or stained only very faintly. Some portions of the necrotic zones were packed with extravasated red blood cells. Poorly demarcated from the tumor foci were occasional small remnants of intact liver parenchyma. Adjacent to the tumor, the

cell cords of the remaining liver lobules merged imperceptibly with those of the tumor. Throughout all portions of the liver were numerous blood vessels that contained clumps of tumor cells within their lumina. In addition to tumor cells, other vessels contained thrombi composed of red blood cells, platelets, fibrin, and polymorphonuclear leukocytes within them. Extending from the endothelial surfaces of these vessels to the peripheral portions of the thrombi were occasional fibroblasts and collagen fibrils.

Examination of the peripancreatic, mesenteric, periaortic, tracheobronchial, and peritracheal lymph nodes revealed all these nodes to be almost completely occupied by collections of tumor cells similar to those within the liver. Areas of necrosis and hemorrhage within the metastasizing tumor aided in altering the original architecture of the nodes so that some were no longer recognizable as lymphatic structures. Where the stroma remained, small islands of hematopoietic cells could be discerned. Normoblasts predominated, but occasional erythroblasts could also be seen.

The marrow spaces of the vertebrae, ribs, and sternum were filled with irregular collections of tumor cells. Where these areas were not occupied by tumor, they were packed with adult red and white blood cells in proportions approximating those of the peripheral blood. Only a few small areas of hematopoiesis were still present, and these areas were very hyperplastic and completely filled the spaces between the bony trabeculae with immature blood elements. In some regions, notably the third

FIG. 1. Cross section of the liver showing the primary carcinoma.

FIG. 2. Low-power view of the carcinoma in the liver showing the tumor cells arranged in cords separated by a connective-tissue stroma.

FIG. 3. High-power view of Fig. 2. The pleomorphic character of the tumor cells is evident. The smaller cells arranged in cords resemble liver-cord parenchyma.

FIG. 4. High-power view of a rib showing carcinoma cells in the marrow spaces intermingled with red blood cells.

lumbar vertebra, the bony spicules adjacent to the tumor were eroded by it.

The splenic sinuses were packed with red blood cells to the extent that the reticulo-endothelial stroma in some regions was no longer discernible. Elsewhere it was hyperplastic and contained within it numerous small islands of erythropoietic cells. Among these, normoblasts were the most numerous and conspicuous. Contained within some of the small arteries were clumps of tumor cells similar to those already described in the liver. In addition to the spleen and the intact lymph nodes, the fatty tissue of the body contained small areas of hematopoiesis.

Metastases were also noted in the lung. In addition, the alveoli in some portions were filled with fibrin, polymorphonuclear leukocytes, debris, red blood cells, mononuclear phagocytes, bacterial clumps, and nuclear debris. The blood vessels of the lung and brain contained clumps of tumor cells within their lumina. Surrounding those of the brain were dense collections of extravasated red blood cells. Other structures, although showing no evidence of destruction or alteration of architecture, contained similar tumor-filled vessels within them. Among those were the epididymis, the dura, and the pancreas.

The significant diagnoses included:

1. Primary carcinoma of the liver (hepatoma).
2. Tumor thrombi of the portal, splenic, and pulmonary veins, and of the left middle cerebral artery.
3. Metastases to the lymphatic vessels and veins of the body of the pancreas, to the mesenteric, perigastric, periaortic, mediastinal, and peribronchial lymph nodes, lungs, lumbar vertebrae, rib and sternum, and to the dural covering of the brain.
4. Hemorrhage into the subdural space, brain, stomach, intestines, kidneys, subcutaneous tissue, skin, and bones (including vertebrae and sternum).
5. Hemoperitoneum.

6. Bronchopneumonia of the lower lobe of the right lung with abscess formation.

DISCUSSION

Panmyelopathy as a sequence of skeletal metastases from the primary carcinoma of the liver is indeed rare. A review^{1, 2, 5, 8, 9, 10, 11, 12} of the reported cases failed to reveal the presence of a single instance of this phenomenon and, strangely enough, in one instance a polycythemic response was noted.⁹ The fact that widespread metastases to marrow, whatever the source, can produce severe anemia is well known and would be expected from any tumor or process replacing active marrow.

How extensive this process may be is often difficult to ascertain clinically. The metastases to the bones in many regions are characterized by replacement of the marrow by tumor cells, with little destruction of the bony trabeculae. These bones generally have a normal appearance, and the extent of the involvement or even the entire process may not be visualized by radiography in the absence of bone destruction. This was amply demonstrated in the routine radiographic examination of the ribs and lumbar vertebrae in this case, which, at most, revealed but a suspicious area of involvement in one of the ribs. However, in our case, another mechanism was evidently in operation in addition to the simple mechanical replacement of the marrow by the tumor cells. One of the outstanding features of the marrow at autopsy was its extensive hemorrhagic character. These large hemorrhagic areas reduced, rapidly and extensively, large sections of functioning marrow, thereby aggravating the already existing hemorrhagic tendency. In effect, a vicious cycle was set up that led to a rapid demise of the individual from extensive hemorrhage into vital organs. Unfortunately, during life, the prothrombin time was not determined. The bleeding in this case was probably precipitated by the thrombocytopenia induced by the replacement of the marrow by the tumor cells.

It has been stressed by a number of authors that a striking feature of these neoplasms is the reproduction of tissue resembling hepatic parenchyma in distant metastases. A characteristic of these cells is their ability to carry out the production of bile pigment. Mallory⁷ observed that the metastatic foci show a color change from yellow to green in formalin-fixed tissue. Ewing⁴ stated that bile diminished with increasing anaplasia. In our case, the color change to yellow-green after formalin fixation was observed in the liver, where the neoplasm showed a resemblance to hepatic parenchyma, but was not seen in the metastatic nodules in which the anaplasia had advanced to the stage where there was no resemblance to the original liver parenchyma.

The presence of the large tumor in the

right lobe of the liver would speak for the single rather than the multicentric origin in our case. The other nodules in the liver were of a much more anaplastic character and did not turn green in formalin. We believe that these were metastatic foci.

SUMMARY

A case of primary carcinoma of the liver, without an accompanying cirrhosis, with widespread metastases to the skeletal system and with resultant myelophthysis is reported. Of considerable interest from a morphological standpoint was the extensive hemorrhage into the bone marrow that appeared coincident to the myelophthitic process and that undoubtedly further aggravated it by the rapid destruction of marrow that came in its wake.

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STEROID EXCRETION IN PATIENTS RECEIVING ANTIFOLIC ACID COMPOUNDS

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and ROGER A. LEWIS, M.D.

VARIOUS antifolic acid compounds have been shown to retard the growth and markedly alter the histological appearance of a transplantable animal tumor (sarcoma 180).¹⁶ These observations with the 4-amino substituted derivative of folic acid, aminopterin and the 4-amino-N¹⁰-methyl derivative, amethopterin, have been repeatedly confirmed with various tumors in different host species.^{9, 13, 14, 17}

The marked alterations observed in the animal tumors following aminopterin administration with dosages that resulted in little evident change in the normal tissues indicate that study of the mechanism of action of this group of antimetabolites might be profitable. It was hoped that a metabolic process of importance to the development of neoplastic cells, but qualitatively or quantitatively less important to normal tissues, might be characterized and defined.

In addition to cytochemical studies in progress, our investigations have shown that the aminopterin effect on the sarcoma 180 could be progressively and completely reversed through the prior administration of folic acid to mice.⁴ No evidence of inhibition as measured by growth in tissue culture or metabolic respiratory studies¹⁵ was

observed when the neoplastic tissues were exposed in vitro to aminopterin-containing solutions. Alterations observed in the neoplasm appear to be secondary to changes induced in the host by the administration of the antimetabolite.

During the course of toxicity studies, a distinct difference in mortality between male and female mice (Carworth Farms—CF 1) was consistently observed. The acute LD₅₀ for male mice was 1.9 mg. per Kg., while that for female mice was 4.9 mg. per Kg. An attempt to reduce this differential sex toxicity with estrogen and androgen administration revealed no essential change, although slight inhibition of toxicity with estrogen and augmentation of toxicity with androgen appeared to be present.³

Others have reported that aminopterin blocked the specific action of estrogen on the female generative tract of the chicken, rat, and frog,^{5, 6, 8} and the castrate rat prostate,¹ while the action of androgen was not affected. In numerous experiments in mice, we have been unable to demonstrate any inhibition of estrogen activity by aminopterin.

As an extension of studies on the mechanism of action of the folic acid antagonists, a selected group of patients was treated with aminopterin or amethopterin for periods of twelve days to six months. These patients were observed for changes in the neoplasm, hematologic status, serum sulfhydryl, and other chemical studies of the blood as well as for evidence of drug toxicity. The excretion of follicle-stimulating hormone (FSH) in the urine as an index of pituitary activity was measured. In addition, because of the possible relationship to estrogen activity, excretion of various steroids was also included in this study. The

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These investigations were aided in part by a grant from the American Cancer Society recommended by the Committee on Growth of the National Research Council and by an institutional grant to the Johns Hopkins University School of Medicine.

The antifolic acid compounds, aminopterin (Lot No 7-8874, 7-8751 and 7-9012) and Amethopterin (Lot No 7-8409A and 7-8687A), were kindly supplied by Dr. R. J. Seeger of the Lederle Laboratories Division, American Cyanamid Company.

Presented in part before the Committee on Growth of the National Research Council, May 23, 1949.

Received for publication, January 13, 1950.

urinary excretion of estrogen, 17-ketosteroids, and 11-oxysteroids (corticosteroids) were serially determined. The patients on whom these hormonal studies were performed included four who had metastatic mammary carcinoma and two with ovarian cancer with generalized abdominal metastases. One patient who had no cancer was also investigated. This last patient was treated with aminopterin for disseminated lupus erythematosus. The changes in the excretion of corticosteroids noted after the administration of the antimetabolites is of such nature that it is deemed of interest to report these at this time. All the determinations were performed in one laboratory.

Determinations of the estrogens and follicle-stimulating hormone were performed on twenty-four-hour urine samples without preservative and the 17-ketosteroids and 11-oxysteroids were performed on twenty-four-hour samples acidified with 5 to 10 ml.

of concentrated hydrochloric acid. The specimens were taken to the laboratory immediately after the daily collection and were refrigerated during the twenty-four-hour intervening period.

The estrogen content of the urine was determined fluorometrically in a Coleman 12 A fluorometer according to the method of Jailer.¹¹ The amount excreted in normal women varies between 10 to 40 µg. per day. Follicle-stimulating hormone was determined by bioassay in 21-day-old female mice. In the low or normal range, the hormone was first precipitated with ethanol and dialysed. A positive result was manifest by enlargement of the uterus. The normal range of values for adult females with this method is 6 to 52 mouse units per day.¹²

The 17-ketosteroids were determined by a slight modification of Schorr's rapid technique of cold extraction with carbon tetrachloride. The color developed with *m*-ni-

TABLE 1
SUMMARY OF 17-KETOSTEROIDS AND 11-OXYSTERIODS IN THE URINE
OF PATIENTS RECEIVING FOLIC ACID ANTAGONISTS

Patient	Age and diagnosis	Drug	Days treated (cumulative)	Dose per day mg.	Total drug mg.	Urinary steroids in 24-hour sample	
						17-ketosteroids mg.	11-oxysteroids mg.
1. H.L.	63 yrs. Metastatic carcinoma breast	Amethopterin	0	0	0	8.4	0.59
			58	2.5-5	160	5.4	0.04
			99	5	350	3.6	0.14
			126	5-10	525	4.2	0.31
2. B.V.	47 yrs. Metastatic carcinoma breast	Aminopterin	0	0	0	—	—
			79	1	77	2.6	0.20
			118	1	106	4.5	0.08
			Drug discontinued 4½ months				
3. R.W.	47 yrs. Metastatic carcinoma breast	Amethopterin	0	0	0	4.5	0.19
			33	2.5	85	4.2	0.10
			0	0	0	6.9	—
			23	1-2	26	4.1	0.07
4. V.M.	46 yrs. Metastatic carcinoma ovary	Amethopterin	0	0	0	4.8	0.17
			25	5-10	145	3.1	0.21
			0	0	0	4.1	—
			83	1-5	194	4.6	0.13
5. M.B.	63 yrs. Carcinoma breast	Aminopterin	0	0	0	4.6	0.31
			48	1	34	7.4	0.04
			87	0.5	53	7.1	0.20
6. M.M.	36 yrs. Lupus erythematosus disseminata	Aminopterin	0	0	0	2.8	0.40
			12	1	12	4.4	0.09
7. H.E.	50 yrs. Metastatic carcinoma ovary	Amethopterin	0	0	0	4.3	0.42
			13	2.5-5	45	3.9	0.28

trobenzene as described by Callow and Callow was then measured.² The normal values noted in this laboratory for females are 8 to 16 mg. per day with this method. The corticosteroids (11-oxysteroids) were determined by extraction of the acidified urine with chloroform, benzene-water partition, and Girard separation as described by Talbot.¹⁸ The color was estimated by employing Heard's technique.⁷ The values for normal male and female adults usually observed are 0.4 to 0.8 mg. per day.

The observations on the urinary excretion of 17-ketosteroids and 11-oxysteroids of patients who received aminopterin or amethopterin are summarized in Table 1. There was no consistent change or deviation in the excretion of follicle-stimulating hormone. One patient (M.M.) with disseminated lupus erythematosus had less than 6.5 mouse units per day in her urine. This was observed both before and during the period of aminopterin administration. Another patient (V.M.) whose twenty-four-hour urinary excretion, before any antimetabolite therapy, was 26 mouse units in twenty-four hours, showed less than 6.5 units one and three months later while receiving amethopterin.

Estrogen excretion was found to be in the normal range before, during, and after the antimetabolites were administered. No consistent deviations within this range were observed. The 17-ketosteroids were low or in the low normal range before any antimetabolite had been administered. After treatment the 17-ketosteroids rose somewhat in three patients, were essentially unchanged in two patients, and fell in two patients. None of the values, in those that showed increases during this period of drug administration, exceeded the low normal value. When one considers the normal variations encountered, the values are fairly stable.

The excretion of 11-oxysteroids was in the low normal range in the four patients in whom pretreatment values were obtained. Following the administration of aminopterin or amethopterin, the values

for 11-oxysteroids in the twenty-four-hour urine samples fell appreciably. In three patients, in whom only posttreatment specimens were available, the 11-oxysteroid excretion was unusually low. The reduction in 11-oxysteroids was noted as early as two weeks after the administration of the antimetabolites was instituted. In two patients, later posttreatment specimens contained more 11-oxysteroids than preceding specimens but did not return to pretreatment levels. One patient, whose urinary 11-oxysteroids were 0.08 mg. per twenty-four hours after 106 mg. of aminopterin, had 0.19 mg. per twenty-four hours four and one-half months after treatment had been discontinued. Thirty-three days later, when 85 mg. of amethopterin had been given, the urinary excretion was 0.10 mg. per twenty-four hours. Another patient with a daily urinary excretion of 0.07 mg. after receiving 26 mg. of aminopterin, showed a level of 0.17 mg. three weeks after treatment was interrupted. Subsequently, 125 mg. of amethopterin was administered over a period of twenty-five days to this patient, at which time the urinary excretion of 11-oxysteroids was 0.21 mg. The increase in the excretion of 11-oxysteroids noted in some patients on prolonged treatment was not associated with reduction in dosage of the antimetabolite or evident clinical improvement in the patient.

No change in the excretion of the 17-ketosteroids consistently accompanied the reduction in the excretion of the 11-oxysteroids. Determination of the fasting blood sugar and serum sodium and potassium levels in two patients did not indicate any evidence of corticoid hypofunction.

Various manifestations of drug toxicity were observed in this small group of patients. Alopecia occurred in one patient after two months of treatment with aminopterin (B.V.). Stomatitis was seen in all patients treated with aminopterin and several of the patients (H.L., VMc. and H.E.) who received amethopterin. Abdominal cramps and nausea were universally experienced at some time by the patients re-

ceiving these drugs. The administration of amethopterin or aminopterin was discontinued for only a few days when the stomatitis appeared and was reinstituted at a lower daily amount thereafter.

The reduction in the excretion of 11-oxy-steroids observed, following the administration of the folic acid antagonists, is unique in that it was not accompanied by a reduction in the excretion of the 17-ketosteroids. When testosterone is administered to patients, a fall in the 11-oxy-steroid excretion is accompanied by a rise in the 17-ketosteroids excreted, but this is exogenous androgen. When methyl testosterone is given, there is a parallel fall in the excretion of 11-oxy-steroids and 17-ketosteroids.

Whether the folic acid antagonists alter the metabolism of corticoid hormone, inhibit its formation, or increase the host requirements is unknown. Higgins has observed that the administration of a potent folic acid antagonist, 4-amino-pteroylglutamic acid (amino-teropterin), in toxic doses to rats was followed by enlargement of the adrenals, and diminution in the size and relative weight of the spleen and thymus gland. The changes in the spleen, thymus, and bone marrow induced by this folic acid analogue were considerably reduced when it was administered to adrenalectomized rats.¹⁰ Further study of the possible relationship of the adrenal steroids to the mode of action of the folic acid antagonists would be fruitful.

A chemical method has been employed for these determinations of the 11-oxy-steroids and 17-ketosteroids. It is recognized that the chemical methods are specific only for certain chemical groups and do not measure the physiological functions exhibited by the characteristic steroids. A method in which the corticoids are determined by bioassay should be employed to confirm these observations.

SUMMARY

Seven patients were given folic acid antagonists. Six patients had cancer and one, generalized lupus erythematosus. The urinary excretion of follicle-stimulating hormone, estrogen, 17-ketosteroids, and 11-oxy-steroids was studied. No consistent change or abnormality was noted in the excretion of follicle-stimulating hormone or estrogen. The excretion of 17-ketosteroids was low in these patients before treatment was instituted, but no significant change followed the administration of the folic acid antagonists. The excretion of 11-oxy-steroids was low normal in four patients before treatment was begun. In all seven patients, the values noted following treatment were below normal. No evidence of adrenal insufficiency was observed in these patients. These observations suggest an interrelationship between the corticoid hormones and folic acid antagonists of possible importance in the study of the mechanism of action of these antimetabolites.

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sponse are mediated have received little clarification.

In view of the biological and clinical interest in folic acid and the folic acid antagonists as therapeutic agents, an investigation of the sex difference in toxicity to aminopterin was instituted. Experiments were designed (1) to determine the influence of sex and age on toxicity, (2) to investigate the influence of sex-hormone administration on toxicity in both immature and mature animals, and (3) to study the effect of ablation of the adrenals or the testes on the toxicity of aminopterin.

METHODS

The experiments were conducted with Carworth Farm (CFI), CFW, and dba mice of both sexes. (The CFW and dba were National Cancer Institute strains) Castate adult males of the CFW and dba strains, and adrenalectomized CFW mice of both sexes, were employed in several experiments. The mice were kept at an environmental temperature of 72° to 79° F., were offered water and food ad libitum, and were weighed daily. In experiments employing sexually mature mice, animals were selected weighing 18 to 24 gm., 2 to 3 months of age. Weanlings 4 weeks of age and weighing 8

to 12 gm. were selected for the experiments with immature mice. Mice selected for orchiectomy and adrenalectomy weighed 20 to 25 gm. Operative procedures were performed under light ether anesthesia, and the mice were allowed to recover for a minimum of seven days prior to injection. Fresh solutions of aminopterin were administered in 0.9 per cent saline. Estrogen and testosterone were suspended in sesame oil. All preparations were injected in a volume of vehicle equal to 1.0 per cent of animal weight. In experiments with CFI mice, the drugs were administered intraperitoneally, while with CFW mice, the subcutaneous route of administration into the axillary space was employed. The sex hormones were administered either concomitantly with aminopterin or on a schedule involving prior and subsequent treatment, as indicated in the individual experiments. Weight change and mortality were observed for a period of ten days following the administration of the folic acid antagonist.

RESULTS

Data describing the acute toxicity of aminopterin at ten days following a single dose in adult CFI and CFW mice are summarized in Table 1 and graphically repre-

TABLE 1
ACUTE TOXICITY OF AMINOPTERIN IN MALE AND FEMALE MICE

Dosage of aminopterin mg/Kg	Mortality* = No dead/Total no treated							
	CFW Adult†							
	CFI Adult†		Intact		Adrenalectomized‡		CFW Immature‡	
	Male	Female	Male	Female	Male	Female	Male	Female
10.0	—	—	18/20	7/20	9/10	8/9	—	—
8.0	—	—	8/10	5/10	10/10	9/10	8/10	10/10
7.5	—	—	9/10	4/10	—	—	—	—
6.0	9/10	5/10	7/10	7/10	5/10	9/10	20/20	19/20
5.0	11/20	13/20	10/20	5/20	—	—	9/9	10/10
4.0	25/30	14/30	3/10	1/10	5/10	5/9	17/20	19/20
3.0	21/30	8/30	8/10	1/10	—	—	14/24	11/21
2.5	14/30	8/30	—	—	—	—	—	—
2.0	4/5	1/5	1/10	0/10	—	—	20/33	18/33
1.5	13/30	4/30	—	—	—	—	—	—
1.0	13/35	1/35	1/10	0/10	—	—	10/25	4/24
0.5	1/35	2/35	0/10	0/10	—	—	2/34	4/30
0.2	—	—	—	—	—	—	0/18	0/20
0	1/50	0/50	0/10	0/10	—	—	0/20	0/20
Estimated LD ₅₀ ± 1 S.E. mg/Kg	1.9 ± 0.2	4.2 ± 0.5	4.2 ± 0.3	7.4 ± 0.6	4.7 ± 0.6	4.5 ± 0.4	1.8 ± 0.2	2.0 ± 0.2
Ratio LD ₅₀ Male Female	1 : 2.2		1 : 1.8		1 : 1		1 : 1.1	

* At ten days postinjection

† Drug administered as a single injection intraperitoneally

‡ Drug administered as a single injection subcutaneously

§ Bilateral adrenalectomy. Male and female mice subjected to sham adrenalectomy showed a sex difference in toxicity similar to intact adults.

TABLE 3
EFFECT OF TESTOSTERONE PROPIONATE
ON THE ACUTE TOXICITY OF AMIN-
OPTERIN IN ADULT CF1 MICE*

Amin- opterin mg./Kg.	Mortality = No. dead/Total no. treated			
	Male		Female	
	Amin- opterin	Amin- opterin +testost.	Amin- opterin	Amin- opterin +testost.
6	6/7	10/10	4/10	4/7
5	6/7	9/10	5/7	5/7
4	9/10	7/10	5/7	3/5
3	9/10	10/10	5/7	3/5
2	7/10	10/10	1/7	3/5
1	3/7	2/3	1/10	1/5
Est. LD ₅₀ ±1 S.E. mg./Kg.	1.5 ±0.3	1.5 ±0.2	3.6 ±0.5	3.2 ±0.6

* Aminopterin was administered as a single injection I.P. Testosterone was administered as a single injection I.P. at 10 mg./Kg.; Neo-Hombreol, Roche-Organon, Inc., Nutley, N.J. was employed. The drugs were administered simultaneously. Mouse weight ranged from 18 to 24 gm. Saline-, testosterone-, and sesame-oil-treated controls showed no mortality.

ble to the toxic effects of single dosages of aminopterin than were intact male mice. In one experiment, four of nine intact mice and one of seven orchietomized mice died after a single subcutaneous injection of 4 mg. per Kg. of aminopterin. In a second experiment with animals of slightly greater age, three of ten intact mice succumbed as contrasted to none of ten orchietomized mice after a single injection of 6 mg. per Kg. of aminopterin. However, these differences were not obtained when similar experiments were repeated employing CFW mice of comparable age and weight.

The sex difference in toxicity was not apparent in adult adrenalectomized CFW mice (Table 1). The estimated LD₅₀ for males was 4.7 mg. per Kg., while that for females was 4.5 mg. per Kg. Male and female

mice subjected to sham adrenalectomy showed a consistent sex difference in the toxicity to aminopterin as did intact controls (Table 1).

DISCUSSION

In these experiments, a greater susceptibility to the toxicity of an antifolic acid compound (aminopterin) was repeatedly observed in mature males when compared to mature females. The sex difference in toxicity for weanling mice was found to be reduced as compared to the two-fold difference in adult mice. Because of the observations of a sex difference in mature mice, it seemed worth while to determine whether the action of the antimetabolite could be differentially influenced by androgens and estrogens. A relationship of sex hormones to folic acid metabolism had been suggested by Hertz's observation that the estrogen-induced growth response in the chick oviduct and rat uterus^{10, 11} was inhibited after administration of aminopterin and other antifolic acid substances. In the rat prostate, Brendler reported that aminopterin interfered with the atrophic action of α-estradiol, but did not prevent stimulation by androgen or reverse the atrophic effect of castration.

In our experiments, estrogen administration was associated with a moderate reduction in the toxicity of the antimetabolite in immature and mature males but was without any effect in immature or mature females. When testosterone was administered

TABLE 4
EFFECT OF ESTRADIOL AND OF TESTOSTERONE ON THE ACUTE TOXICITY
OF AMINOPTERIN IN IMMATURE CFW MICE*

Aminopterin mg./Kg.	Mortality = No. dead/Total no. treated					
	Male			Female		
	Aminopterin	Aminopterin +estrogen	Aminopterin +testosterone	Aminopterin	Aminopterin +estrogen	Aminopterin +testosterone
6.0	20/20	10/10	10/10	19/20	9/10	9/10
4.0	17/20	6/10	8/10	19/20	5/10	10/10
2.0	14/19	5/10	7/10	11/19	6/10	5/10
0.5	2/19	0/10	0/19	3/20	3/10	5/10
0.2	0/18	0/10	1/10	0/20	1/10	0/10
Est. LD ₅₀ ±1 S.E. mg./Kg.	1.5 ±0.3	2.5 ±0.4	1.6 ±0.4	1.8 ±0.3	1.8 ±0.6	1.6 ±0.4

* Aminopterin was administered as a single subcutaneous injection on 0 day, Estradiol (10 mg./Kg.) and testosterone (10 mg./Kg.) were administered subcutaneously on days: -4, -3, -2, -1, 0, 1, 2. The mice weighed 8 to 12 gm. and were less than 21 days old. The drugs were administered concomitantly on 0 day. Saline-, estradiol-, testosterone-, and sesame-oil-treated controls showed no mortality.

with the aminopterin, the toxicity of the latter was not significantly altered in either immature or mature males and females. In no instance was the sex difference in the toxicity of aminopterin to adults obliterated by the administration of a single synthetic steroid hormone associated with the opposite sex. These findings are in accord with established observations that neither estradiol nor testosterone are capable of replacing the complete steroid complement responsible for the differences of sex.⁷

In two successive experiments, mice of the dba strain showed a greater tolerance to aminopterin after castration. This result, however, could not be repeated in mice of the CFW strain. Studies are in progress to determine whether this apparent inconsistency was related to the established strain differences in the rate of involution of the "x-zone" of mouse adrenal glands.¹³

The failure to maintain a differential sex toxicity to the antifolic compound, aminopterin, after adrenalectomy suggests a possible role of the adrenal gland in folic acid metabolism. Observations of other investigators indicate, indirectly, that a differential sex toxicity of the type observed in our experiments could be related to sex differences in function and morphology of the adrenals. A greater resistance to the toxic effects of whole adrenal cortical extracts¹⁴ and compound E²⁴ has been demonstrated in female rats as compared to male rats. Ingle suggested that the differential sex toxicity to adrenal extract was related to the relatively larger amount of cortical tissue in the adrenal glands of females as compared to males. The adrenals of females were grossly larger soon after birth. This difference persisted throughout life even when females and males were castrated at birth.¹⁴ Female mice have also been reported to show a more rapid regression of a transplantable lymphosarcoma, when compared to males, after treatment with compound E.⁹ Of possible interest are the observations of a sex difference in the morphology of mouse adrenals. In several mouse strains, the region of the "x-zone" has been reported¹³ to persist in

virgin females throughout life, whereas in other strains rapid atrophy was found. Males showed a fairly consistent involution of the "x-zone" within a relatively short period after reaching maturity. Studies of the influence of adrenal hormones on the toxicity of antifolic substances are in progress.

A differential effect on the adrenal steroids has also been recently observed in studies^{19, 20} of patients treated for metastatic cancer with aminopterin. Patients receiving prolonged aminopterin therapy showed reduction in the excretion of reducing corticoids (11-oxysteroids) without significant alteration in excretion of 17-ketosteroids or estrogens. The mechanism of action of aminopterin thus appears to be related in some way to the metabolism of the adrenal steroids. Higgins¹² has observed a hypertrophy of the adrenals of rats after aminopterin treatment. The selective effect of aminopterin on reducing corticoids in man and the differential sex toxicity established in mice suggest that the adrenal hypertrophy observed by Higgins may not be entirely a manifestation of a generalized "stress" reaction. Under conditions of stress, the excretion of glycogenic (reducing) corticoids in the urine is usually found to be increased together with the 17-ketosteroids. In contrast, the finding of a decrease in 11-oxysteroids in patients receiving aminopterin therapy, with no parallel change in the excretion of the 17-ketosteroids, is unique.²⁰

Although the evidence presented suggests that the adrenals may be intimately concerned with folic acid metabolism, this evidence is essentially indirect. The sex difference in toxicity to aminopterin could be a reflection of a differential rate of excretion of substances involved in folic acid metabolism. The sex differences in morphology of kidney tubules and glomeruli and in the concentration of alkaline phosphatase³ could likewise play some role in this phenomenon, especially since certain renal enzymes in mice have been reported to be readily influenced by castration and by steroid hormones.³

In other studies,⁵ we have shown a progressive and complete inhibition of aminopterin toxicity by the administration of folic acid at a requisite interval (one hour) prior to the injection of aminopterin. When this interval was employed, the optimal ratio of folic acid for complete protection against several supralethal levels of aminopterin was found to be constant at approximately 2:1. In males, a greater amount of folic acid was necessary to block the aminopterin than in females. Taylor and Carmichael have recently reported that large doses of folic acid itself were more toxic to females than males (dba strain). The greater toxicity of folic acid to female mice reported by them and the greater tolerance of females to the antifolic (aminopterin) in our experiments are complementary. The mechanism through which the sex difference in tolerance to folic acid and its antagonist is mediated is unknown. Whether the difference in toxicity is due to a greater reserve of folic acid in the females, a lesser requirement for folic acid, or more rapid excretion of the antagonist cannot be determined from these data, which, however, are

consistent with these hypotheses. From our present knowledge, it would seem most probable that the differential sex toxicity of aminopterin is mediated in part at least by sex differences in adrenal steroid metabolism. Future studies may indicate a more direct role of adrenal metabolites in the folic acid metabolism of the intact mammal.

SUMMARY

A two-fold sex difference in the lethal toxicity of the folic acid analogue, aminopterin, was demonstrated in adult mice of the CF1 and CFW strains. Males showed reduced tolerance when compared to females. In immature mice, sex differences were not apparent. The administration of estrogen to immature and adult males increased the tolerance to aminopterin. Testosterone failed to influence toxicity in males or females. Bilateral adrenalectomy eliminated the differential sex toxicity of aminopterin. The possible significance of the relationship of the aminopterin effect to folic acid and adrenal steroid metabolism is discussed.

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STUDIES ON THE MECHANISM OF ACTION OF CHEMOTHERAPEUTIC AGENTS IN CANCER

II. *Requirements for the Prevention of Aminopterin Toxicity by Folic Acid in Mice*

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THE competitive antagonism of 4-amino-pteroylglutamic acid (aminopterin) to pteroylglutamic acid (folic acid) was initially established on the basis of the in vitro inhibition of pteroylglutamic acid as an essential metabolite for the growth of bacteria.^{10, 13} However, the inhibition index of aminopterin employing *Streptococcus faecalis* R was found to vary widely over a range of metabolite concentrations.¹⁰ From observations on both bacterial and animal growth, Oleson et al. concluded that the inhibition of folic acid by aminopterin was not of a strictly competitive nature. (Inhibition index = Ratio of molar concentration of antagonist to that of the metabolite necessary to demonstrate 50 per cent inhibition of growth in a standard culture of *S. faecalis* R.)

Partial reversal of the systemic toxicity of aminopterin by folic acid in mice and rats has been reported by a number of investigators.^{4, 7, 10, 11, 12} In these studies, diverse quantitative and temporal relationships of metabolite and antagonist were employed as well as different routes of administration. Thiersch and Philips concluded in a

review of the present status of antifolic compounds that aminopterin differed from an ideal antimetabolite in mice,^{4, 11, 12} rats,^{7, 10} and chicks,¹⁰ in that its toxicity was "not readily prevented or reversed by folic acid."

Complete reversal of the tumor-inhibiting action of aminopterin has been observed after repeated injections of folic acid in mice bearing transplantable sarcoma³ and transmissible leukemia.⁹ Partial reversal of the aminopterin-induced inhibition of a mammary carcinoma⁸ in mice has also been reported. In patients with leukemia, however, large doses of folic acid have been found to be incapable of reversing the toxic effects of aminopterin.^{1, 3}

In view of the lack of precise information with regard to the competitive relationships of aminopterin and folic acid in mammals, further studies of this metabolite antagonism were believed warranted. These experiments were undertaken (1) to clarify the quantitative relationships in the metabolite antagonism of aminopterin to folic acid, (2) to investigate the temporal conditions necessary for the prevention of aminopterin toxicity by folic acid, and (3) to determine whether the sex difference in the toxicity of aminopterin observed in our laboratory⁶ could be correlated with folic acid metabolism.

METHODS

CFW, C3H, dba, and A mice of the National Cancer Institute strains were employed in these experiments. The mice were housed in plastic cages and received Purina

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These investigations were aided in part by a grant from the American Cancer Society to the Department of Preventive Medicine, The Johns Hopkins University School of Medicine, recommended by the Committee on Growth of the National Research Council.

Aminopterin (Lederle Lab. No. 7-8751) and folic acid (Lederle Lab. No. 53106-3) were obtained from the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York. The purity of folic acid was stated to be 90 per cent.

Received for publication, April 7, 1950.

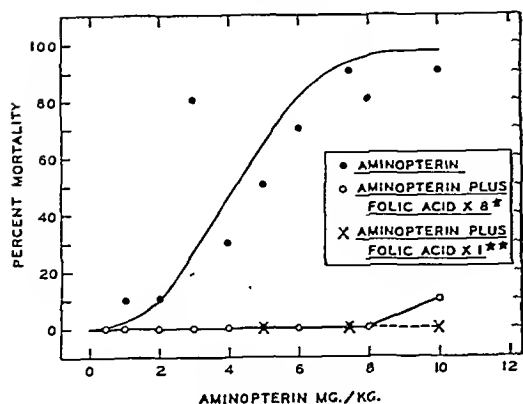


FIG. 1. Reversal of aminopterin toxicity by prior administration of folic acid. Mortality at ten days after injection. CFW male mice; ten to twenty mice per group. All injections, subcutaneously. Aminopterin dissolved in n-saline; folic acid dissolved in 2 per cent sodium bicarbonate solution. *Eight injections of folic acid. The schedule in days was $-4, -3, -2, -1, 0, 1, 2, 3$. On zero day, the folic acid was administered one hour prior to injection of aminopterin. **One injection of folic acid administered on zero day, one hour prior to administration of aminopterin. Eight injections of sodium bicarbonate on the same dosage schedule as folic acid $\times 8$, plus a single injection of aminopterin, gave the same result as aminopterin alone. In other experiments (see Table 1), mortality was evident at 100 mg. per Kg. folic acid.

chow and water ad libitum. They were maintained at 72° to 78° F. prior to and during the course of the experiments. Mice of each sex were selected for uniformity of age and weight in the individual experiments. Subcutaneous injections were administered into the axillary space. Contralateral axillae were selected to avoid direct mixing of the agents when more than one drug was employed. Intravenous injections were administered into a lateral tail vein. Fresh solutions of aminopterin in 0.9 per cent saline and folic acid in 2 per cent sodium bicarbonate solution were prepared immediately prior to each injection period. The total volume of diluent for each injection was maintained at 1 per cent of the body weight. Appropriate controls were

employed for each experiment. The mice were observed for mortality, and survivors were weighed daily during the course of an experiment. All experiments were terminated ten days subsequent to the administration of aminopterin. The studies on the peripheral blood were conducted with blood obtained from the tail vein. Dosage schedules are indicated in the experiments cited.

RESULTS

Complete protection against a single supralethal subcutaneous dose of aminopterin (10 mg. per Kg.) was observed in CFW mice of both sexes treated with a series of subcutaneous injections of folic acid (25 mg. per Kg.), when the folic acid was administered on a daily schedule including treatment prior to and subsequent to the injections of aminopterin. The results of an experiment employing male mice are summarized in Fig. 1. The median lethal dose (LD_{50}) in adult CFW mice was reported previously⁶ to be approximately 4.2 mg. per Kg. for males and 7.2 mg. per Kg. for females. Complete protection was provided also by a single dose of folic acid when it was injected subcutaneously one hour prior to aminopterin (Figs. 1, 2). However, no protection was observed when the folic acid was given simultaneously with

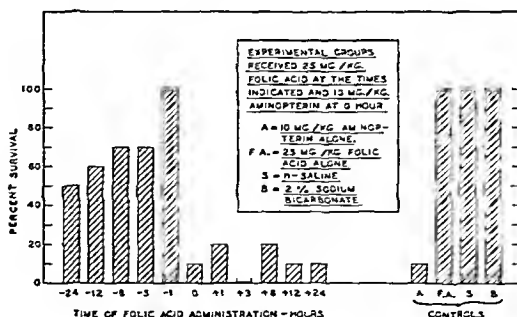


FIG. 2. Temporal relationships in the reversal of aminopterin toxicity by folic acid. Survival at ten days after injection of aminopterin. CFW male mice, ten mice per group. All injections, subcutaneously. Aminopterin dissolved in n-saline; folic acid dissolved in 2 per cent sodium bicarbonate solution.

the lethal dose of aminopterin (Fig. 2).

These observations suggest that the time relationships may be of considerable importance in the competition between the metabolite and antagonist. The results of an experiment designed to test this relationship are summarized in Fig. 2. Each animal group was treated with a single injection of folic acid (25 mg. per Kg.) at intervals ranging from twenty-four hours prior to twenty-four hours following the administration of the aminopterin (10 mg. per Kg.). It was found (Fig. 2) that no protection was afforded by this ratio (2.5:1) unless the folic acid was injected prior to the aminopterin. Maximal protection was obtained when the folic acid was administered one hour prior to the aminopterin. Protection diminished progressively (Fig. 2) when folic acid was given at earlier intervals than one hour (three, eight, and twenty-four hours prior to the administration of aminopterin). Only 50 per cent protection was observed when the folic acid was administered twenty-four hours prior to the aminopterin. In additional experiments, diminished protection was also evident when folic acid was administered at thirty, fifteen, or five minutes prior to the aminopterin. Higher doses of folic acid, administered subcutaneously, concomitantly with or following a subcutaneous injection of aminopterin, provided no protection against the toxicity of the antagonist. No protection was afforded upon simultaneous administration even when the ratio of folic acid to aminopterin was progressively increased from 25:1 to 10:1 (100 mg. per Kg. folic acid:10 mg. per Kg. aminopterin). In none of these experiments was there any evidence that the sodium bicarbonate solution (the vehicle for folic acid) contributed to the prevention of the aminopterin toxicity.

Experiments were performed to estimate more precisely the concentration of folic acid, administered as a single dose, required to inhibit the toxicity of a single dose of aminopterin. As a representative supra-lethal dose of aminopterin, 10 mg. per Kg.

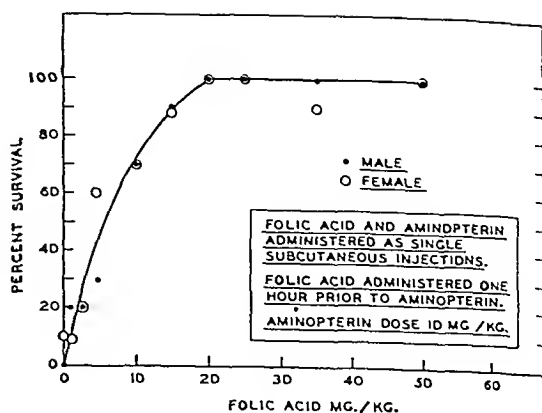


FIG. 3. Progressive reversal of aminopterin toxicity by prior administration of folic acid. Survival at ten days after injection. CFV mice; all injections, subcutaneously. Sixty mice of each sex employed at the dose 5 mg./Kg. folic acid plus ten mg./Kg. aminopterin. Ten mice of each sex employed at each of the other dose levels. Aminopterin dissolved in n-saline; folic acid dissolved in 2 per cent sodium bicarbonate solution. Controls receiving folic acid (1 mg./Kg. to 50 mg./Kg.), saline, sodium bicarbonate solution, and saline plus sodium bicarbonate, showed 100 per cent survival.

was selected. Folic acid was administered at a series of concentrations ranging up to 50 mg. per Kg. Folic acid was administered one hour prior to aminopterin in all instances, since such a temporal relationship, as already indicated, appeared to offer optimal protection. Both aminopterin and folic acid were administered subcutaneously. The study was performed with each sex, since a differential sex toxicity to aminopterin has been repeatedly observed.⁶ The data are summarized in Fig. 3. Complete protection was obtained with doses ranging from 20 mg. per Kg. to 50 mg. per Kg. of folic acid. Below 20 mg. per Kg. of folic acid, a progressive decline in protection was observed. Fifty per cent protection (combined data for both sexes) was estimated to occur when 10 mg. per Kg. of aminopterin and 5 to 6 mg. per Kg. of folic acid were employed. Analysis of data by sex showed a higher requirement, in the LD₅₀ range, for equivalent protection with folic

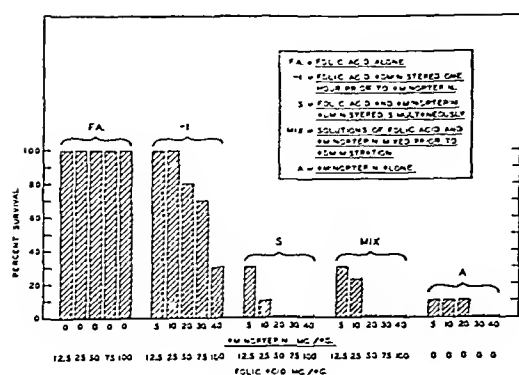


FIG. 4. Prevention of aminopterin toxicity by the prior administration of constant ratios of folic acid. Survival at ten days after injection. CFIV male mice; ten mice per group. All injections, subcutaneously. Aminopterin dissolved in n-saline; folic acid dissolved in 2 per cent sodium bicarbonate solution.

acid among males when compared to females (Fig. 3).

As noted above, 25 mg. per Kg. of folic acid offered consistent protection against 10 mg. per Kg. of aminopterin when the folic acid was administered one hour prior to injection of aminopterin. Employing this ratio of folic acid to aminopterin (2.5:1), an experiment was performed to determine to what extent the prevention of toxicity was maintained at stoichiometric proportions over an extended range of lethal concentrations of aminopterin. The results are presented in Fig. 4. With folic acid administration one hour prior to the aminopterin, there was complete protection at doses of 12.5 and 25 mg. per Kg. of folic acid with doses of 5 and 10 mg. per Kg. of aminop-

TABLE 1
TOXICITY OF FOLIC ACID

Folic acid* mg./Kg.	Aminopterin mg. Kg.	Mortality
225	—	4/8
200	—	6/17
100	—	1/18
200	10	4/10
100	10	2/10
25	10	0/10

* Folic acid administered at minus one hour, subcutaneously. CFIV male mice (20 to 25 gm. body weight).

terin respectively. At 50 and 75 mg. per Kg. folic acid, with 20 and 30 mg. per Kg. of aminopterin respectively, considerable protection was retained. Only slight protection occurred at 100 mg. per Kg. folic acid with 40 mg. per Kg. aminopterin. Toxicity from the metabolite itself (or impurities) began to appear at levels of 75 to 100 mg. per Kg. of folic acid (Table 1). Further studies at the higher dose levels were thus not feasible with the available preparations. Within the dose range in which studies were unaffected by folic acid toxicity, protection was maintained despite doses of antagonist that were approximately four times greater than the LD₅₀.

TABLE 2

EFFECT OF PRIOR ADMINISTRATION OF FOLIC ACID ON AMINOPTERIN TOXICITY IN FOUR STRAINS OF MICE

	Mortality = Dead/Total		
	Prior*	Simultaneous†	Aminopterin alone
CFW	0/10	10/10	8/10
dba	0/10	10/10	8/10
C3H	0/10	10/10	8/10
A	0/10	7/15	—

* Folic acid administered one hour prior to aminopterin.

† Folic acid and aminopterin administered concomitantly. Mice received single subcutaneous injections of each agent. Folic acid was administered at 25 mg./Kg. and aminopterin at 10 mg./Kg. Male mice, (20 to 25 gm. body weight).

The complete protection by folic acid was found to be maintained by the following parenteral routes of administration when the folic acid was given one hour before aminopterin: (1) folic acid and aminopterin subcutaneously; (2) folic acid intravenously, aminopterin subcutaneously; (3) folic acid subcutaneously, aminopterin intravenously; and (4) folic acid and aminopterin intravenously. With none of these combinations of routes of administration was there appreciable protection by simultaneous administration of metabolite and antagonist. Similarly, lack of protection was evident on the immediate successive administration of aminopterin and folic acid by the intravenous route, regardless of the order of administration. Solu-

tions of aminopterin and folic acid mixed prior to administration (Fig. 4) also offered no protection against aminopterin toxicity.

The protection by folic acid and the temporal relationship required for its demonstration were not limited to one strain of mice (Table 2). CFW, dba, C3H, and A mice all showed complete protection by the prior administration of folic acid at the ratio of 2.5:1.0 and the optimal time interval.

When the temporal requirement for protection was met, the ratio of metabolite to antagonist (2.5:1) provided protection (Table 3) for an indefinite period in mice treated at weekly intervals with supralethal doses of aminopterin. However, this ratio (2.5:1) was found to be inadequate for protection when doses of both the metabolite and antagonist were administered at twenty-four-hour intervals. When the folic acid was doubled (ratio 5:1), protection was maintained for two repeated injections (Table 3, Experiment 4) but not for three such injections at twenty-four-hour intervals. At forty-eight-hour intervals, the ratio of 2.5:1 likewise did not result in protection.

The progressive blocking of aminopterin toxicity by increasingly higher concentrations of folic acid was reflected in the general appearance and change in body weight of the animals. Male and female mice that were completely protected by folic acid showed no evidence of the usual

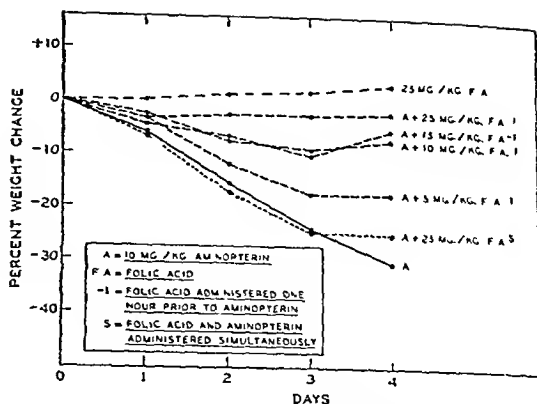


FIG. 5. Reversal of aminopterin-induced weight loss by the prior administration of folic acid. CFW male mice; ten mice per group. All injections, subcutaneously. Aminopterin dissolved in n-saline; folic acid dissolved in 2 per cent sodium bicarbonate solution.

aminopterin-induced syndrome consisting of diarrhea, anorexia, ruffled fur, and weight loss. The full development of this syndrome in unprotected animals was characteristically delayed until the third day after aminopterin injection. The early alterations in body weight are summarized in Fig. 5. The parallelism of weight change to lethality (Figs. 2, 3) was evident. Mice receiving simultaneous doses of 10 mg. per Kg. aminopterin plus 25 mg. per Kg. folic acid lost approximately the same weight as mice treated with aminopterin alone. Mice treated with 25 mg. per Kg. of folic acid one hour prior to 10 mg. per Kg. aminopterin maintained their weight in the same range as the folic acid-treated controls. Lethal concentrations of aminopterin alone elicited peripheral-blood leukopenia (Table 4) and a diminution of erythrocyte polychromatophilia. The prevention of toxicity and weight loss by folic acid administration was accompanied by the absence of leukopenia and the maintenance of erythrocyte polychromatophilia.

DISCUSSION

A wide range of ratios of inhibition has been reported in previous studies on the quantitative aspects of the competition be-

TABLE 3

TOXICITY OF MULTIPLE INJECTIONS OF AMINOPTERIN AND FOLIC ACID*

Exper. no.	Folic acid mg./Kg.	Aminopterin mg./Kg.	No. inject.	Interval, hrs.	Mortality
1	25	10	1	—	0/10
2	25	10	4	24	10/10
3	25	10	2	48	10/10
4	25	5	2	24	0/10
5	25	5	4	24	9/9
6	25	10	6	168	0/10
7	12.5	5	4	24	10/10
8	12.5	5	2	24	4/10
9	16.7	3.3	3	24	6/10
10	8.3	3.3	3	24	5/10
11	5	2	4	24	10/10
12	—	5	1	—	10/10

* At each injection period, folic acid was administered one hour prior to aminopterin. All injections given by subcutaneous route to male mice (20 to 25 gm. body weight).

tween aminopterin and folic acid in animals. Oleson et al. found that multiple daily feedings of 30 mg. of folic acid per kilogram of diet were necessary to provide partial reversal of the toxicity of 1 mg. of aminopterin per kilogram of diet when both agents were administered simultaneously to chicks or rats. A higher ratio of metabolite : antimetabolite was required in the studies reported by Franklin et al. in mice. Partial protection was obtained only by feeding 100 mg. folic acid per kilogram of diet with 0.3 mg. of aminopterin per kilogram of diet. When aminopterin was increased to 1 mg. per Kg. of diet, no protection was observed. Higgins⁷ observed partial protection in rats receiving intraperitoneal injections of aminopterin when amounts of folic acid 100 to 1000 times greater than that of the aminopterin were employed in the diet. When both agents were administered intraperitoneally, Philips and Thiersch found that doses of folic acid approximately four to thirty times greater than those of aminopterin were required to provide partial protection from the antifolic toxicity. On the basis of animal and bacterial work, Oleson's group concluded that aminopterin was not an "ideal" metabolite antagonist since the relationships were not strictly competitive, although they appeared to be partially reversible. Philips and Thiersch also concluded that aminopterin was not an "ideal" antagonist since its actions were not readily prevented or reversed by folic acid. These investigations appear to be difficult to evaluate, since the

influence of temporal relationships on the competition between folic acid and aminopterin was not fully explored.

In the studies reported here, complete protection was observed against the toxic effects of single supralethal dosages of aminopterin in several strains of mice. The degree of protection afforded by folic acid in mice was intimately related to the time of its administration with respect to aminopterin. Complete protection was obtained only when the metabolite was administered within a relatively short period (one hour) prior to but not immediately before or subsequent to the single injection of the antagonist. These temporal conditions were found to be required for protection even when various parenteral routes of administration and several ratios of metabolite to antagonist were employed. Complete protection was observed when a ratio (folic acid : aminopterin) of 2.5:1 was maintained at progressively increasing doses, until toxicity of the folic acid itself became manifest. The determination of an inhibition ratio (metabolite : antagonist) in the intact animal would thus appear to be of little significance, unless the temporal relationships of drug administration are specified. The necessary interval may represent that period during which the mouse converts or incorporates the folic acid into the protective metabolic product. Aminopterin may prevent this conversion.

On the basis of the optimal time relationships and ratios (metabolite : antagonist) for protection observed in our studies,

TABLE 4

BLOOD COUNTS AT SEVENTY-TWO HOURS AFTER SUBCUTANEOUS ADMINISTRATION OF AMINOPTERIN AND FOLIC ACID TO MALE CFW MICE

Aminopterin mg /kg	Folic acid mg /kg	Hb gm /100 cc	R B C./cu mm $\times 10^{-6}$	W B C./cu mm $\pm 1 S E$	Differential		
					Poly	Lymph	Mono
20	0	17 3(2)*	11 5(2)	7460 \pm 1680(5)	63 4(5)	36 4	0 2
20	50	15 8(4)	9 2(3)	13980 \pm 2280(5)	25 8(5)	73 4	0 8
10	1	17 3(2)	10 5(2)	8800 \pm 660(4)	35 0(4)	65 0	0
10	25	15 9(4)	7 7(2)	12550 \pm 2090(4)	24 5(4)	74 5	1 0
10	50	15 8(4)	8 8(2)	11400 \pm 900(4)	27 5(4)	71 0	1 5
0	25	14 9(4)	7 2(2)	11840 \pm 1800(4)	29 8(4)	67 8	2 4
0	50	15 5(4)	9 1(2)	12340 \pm 1720(4)	20 0(4)	79 8	0 2

* Average value for the number of mice indicated in parentheses.

indirect evidence is available with regard to the metabolism of folic acid in the mouse. When the folic acid (25 mg. per Kg.) was administered twenty-four hours prior to the aminopterin (10 mg. per Kg.), rather than at one hour prior to the aminopterin, a 50 per cent loss in protection was observed (Fig. 2). Since the ratio for 50 per cent protection with folic acid administered one hour prior to aminopterin was 5 to 6 mg. per Kg. folic acid to 10 mg. per Kg. of aminopterin (Fig. 2), it may be inferred that approximately 80 per cent of the administered folic acid (25 mg. per Kg.) was metabolized or excreted in the mice during the twenty-four-hour period prior to the administration of aminopterin. During the daily administration of folic acid, sufficient metabolite might be retained, regardless of exact temporal relationships, to provide partial or complete protection from the toxicity of repeated sublethal doses (0.1 to 0.5 mg. per Kg.) of aminopterin. Doses of this magnitude have been employed by various observers,^{5, 7, 9, 10, 11} who have reported a partial or complete "reversal" of the aminopterin effect in tumor-bearing and nontumor-bearing rodents. These results could indicate that protection was afforded by cumulative doses of folic acid. No evidence was presented of reversal of established toxicity.

The absence of a true reversibility, i.e., a failure of successful competition between metabolite and antagonist when these were made simultaneously available to the organism, was observed even when the ratio for protection by folic acid was increased above required limits. For example, the administration of massive amounts of folic acid (50 to 75 mg. per Kg.), and 10 mg. per Kg. of aminopterin failed to interfere with the toxicity of the latter when the two agents were simultaneously administered. Our data suggest that a true reversal of a lethal aminopterin effect may not be obtained by the administration of folic acid, despite the ability of folic acid to block completely or to prevent lethal toxicity of aminopterin.

Mice injected at weekly intervals showed repeated protection from single supralethal doses of aminopterin when the usual ratio and time relationship for single-dose protection was maintained. However, this protection was not obtained when such doses were given at twenty-four- or forty-eight-hour intervals. This observation might indicate that a subthreshold amount of aminopterin remained fixed in the tissues or was more slowly excreted as compared to folic acid. Recent reports suggest that aminopterin may also interfere in the metabolism of glycine and creatine.² The first injection of aminopterin might, therefore, produce an inapparent deficiency or alteration in metabolic factors, despite the protection from lethal toxicity by folic acid. Such an interference in related metabolic processes might be responsible for the failure of folic acid to protect the animal against rapidly repeated supralethal doses of aminopterin. The metabolic state appeared to return to normal within a week, as demonstrated by the protection with the usual dose of folic acid.

The experimental data reported here may be correlated with the clinical experience that folic acid fails to reverse the toxicity of aminopterin. In the normal mouse, aminopterin appears to be unique in the extreme speed with which it may produce an irreversible alteration in an essential metabolic process.

SUMMARY

The influence of folic acid on the toxicity of single supralethal doses of aminopterin was studied in a number of mouse strains. Metabolite: antagonist ratios of 2.5:1 or higher were found to provide complete protection against supralethal doses of aminopterin. An optimal time interval for the demonstration of protection by the administration of metabolite was established as one hour prior to the antagonist. Simultaneous or subsequent administration of metabolite failed to prevent toxicity

from the antagonist, despite the use of various parenteral routes of administration. Increased ratios of metabolite : antagonist failed to reverse toxicity, unless optimal temporal relationships were maintained. Stoichiometric proportions over a range of doses of metabolite : antagonist provided complete protection at doses of antagonist that were three to six times greater than the LD_{50} . At very large doses, the inherent

toxicity to the folic acid preparation itself became evident.

Protection from supralethal doses of aminopterin was obtained repeatedly at weekly intervals, but no protection could be obtained by the daily administration of metabolite and antagonist in the proper dose and time relationships. Possible explanations for these observations are suggested.

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STUDIES ON THE MECHANISM OF ACTION OF CHEMOTHERAPEUTIC AGENTS IN CANCER

III. *Relationship of Genital Growth Response in Mice to the Folic Acid Analogue, 4-Amino-pteroylglutamic Acid*

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A DIFFERENTIAL sex toxicity of 4-amino-pteroylglutamic acid (aminopterin) has been repeatedly demonstrated in the mouse.^{2, 9} Attempts to eliminate this sex difference in toxicity by the administration of estrogen or androgen were essentially without effect.²

Several reports have appeared in which the growth-stimulating action of estrogen on the genital tract has been inhibited by induced folic acid deficiency⁶ as well as by folic acid antagonists.^{7, 8} Hertz^{7, 8} reported inhibition of the estrogen-induced growth response in the chick oviduct and rat uterus by several folic acid analogues, including aminopterin. In rats, this antiestrogen effect was found to cause approximately 50 per cent reduction in uterine weight during a short period of observation after repeated administration of maximum tolerated doses of aminopterin. Partial restoration of estrogen activity was again manifest when pteroylglutamic acid (folic acid) was adminis-

tered in large doses together with the analogue. Employing the oviduct of the newly metamorphosed frog, Goldsmith⁴ observed inhibition of estrogen activity after aminopterin treatment, which could not, however, be restored by the addition of folic acid in ratios as high as 100:1 of folic acid to aminopterin. Brendler found that aminopterin blocked the α -estradiol-induced involution of the rat prostate but did not prevent the atrophic effect of castration. The androgen-induced stimulation of the prostate in castrate-adult or intact-immature rats was reported to be unaffected by aminopterin. The dosage of aminopterin employed approximated the daily maximum tolerated dose (0.2 mg. per Kg.). Goldsmith et al.⁴ obtained interference with testosterone-induced growth response of the seminal vesicles and coagulating glands of testosterone-treated mice by feeding of the N¹⁰-methyl analogue of aminopterin (amethopterin). Although these experiments appear to be in disagreement in certain important details, dependent on species difference, they seem to suggest that folic acid may play some role as an essential factor in the utilization of the estrogens. In view of our observations of a differential sex toxicity of the antifolic compound aminopterin in mice, further studies were instituted in this species in an attempt to elucidate factors of importance in the mechanism of action of this chemotherapeutic agent. This study presents our observations on the effects of aminopterin administration on the activity of estrogenic and androgenic substances as measured by growth changes in the genital organs.

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These investigations were aided in part by a grant from the American Cancer Society to the Department of Preventive Medicine, The Johns Hopkins University School of Medicine, recommended by the Committee on Growth of the National Research Council.

The authors wish to acknowledge the technical assistance of John Venditti, Annie Collins, and Natalie Hill.

Aminopterin (Lederle Lab. No. 7-8871B) and folic acid (Lederle Lab. No. 53106-3) were obtained from the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York. The folic acid was stated to be 90 per cent pure. The source of steroid hormone is indicated with the individual experiments.

Received for publication, April 7, 1950.

MATERIALS AND METHODS

The experiments were performed on mice, employing CFW (National Cancer Institute strain) and Carworth Farms CF1 mice. The mice were individually marked and weighed daily. They were provided with water and food *ad libitum* and kept at an environmental temperature of 72° to 78° F. The drugs were injected either subcutaneously or intraperitoneally, as indicated in the individual experiments. Fresh solutions of aminopterin were prepared prior to each injection period. Estrogen and testosterone were prepared from stock suspensions. Aminopterin, estrogen, and folic acid were so administered that the total volume of diluent was equal to 1 or 2 per cent of the animal's total body weight. The studies on the growth response of the female reproductive tract were made employing adult mice (19 to 22 gm.), immature mice (8 to 14 gm.), and castrate females (19 to 21 gm.).

The following types of experiments were performed: 1. Single lethal dosages of aminopterin were given, followed one day later by a single injection of estrogen. The observations were made two days after estrogen injection. The aminopterin was administered at 5 mg. per Kg. and 3 mg. per Kg., and estrogen in aqueous suspension, at 10 mg. per Kg. 2. Aminopterin (0.3 mg. per Kg. per day) and estrogenic substances were administered on three successive days. The mice were sacrificed three days following the final injection. In this experiment, estrogen aqueous (10 mg. per Kg.), estrogen in corn oil (10 mg. per Kg.), and stilbestrol (10 mg. per Kg.) were employed. 3. Mice received daily injections of 0.3 mg. per Kg. of aminopterin together with estrogen in corn oil (5 mg. per Kg.) for six successive days. The mice were sacrificed four days after the final injections. 4. Aminopterin (0.3 mg. per Kg.) was administered on three successive days followed by estrogen in corn oil (10 mg. per Kg.) administered as a single injection one day following the last aminopterin injection. This experiment was terminated two days following the final injection. 5. Amin-

opterin (0.3 mg. per Kg.) was administered on three successive days and estrogen (10 mg. per Kg.) in corn oil on the two days following aminopterin treatment. This experiment was terminated two days following the final injection. 6. Aminopterin at two dosages (0.3 mg. per Kg. and 0.2 mg. per Kg.) was administered on three successive days. Estrogen (10 mg. per Kg.) was given on the second and third day and the mice were sacrificed two days later. 7. Folic acid (25 mg. per Kg.) was administered on four successive days; aminopterin (0.3 mg. per Kg.) was administered on the last three days while estrogen (0.75 γ per Kg.) was injected twice daily for the last two days. The uterine weight was obtained one day following the final injection.

The mice were sacrificed by cervical dislocation. Following excision, the wet weight of the uterus, ovaries, and oviducts were determined in nonovariectomized mice. The wet weight of the uterus only was determined in ovariectomized mice.

The response of the seminal vesicle in male mice was also studied. Immature CFW mice were employed (8 to 12 gm.). Aminopterin was administered for three successive days and α -estradiol or testosterone propionate was administered on the second and third day. The seminal vesicles were excised and wet weight determined forty-eight hours following the last injection. Appropriate controls were employed in all of the experiments.

RESULTS

In the seven experiments outlined, no inhibition of the estrogenic growth response of the reproductive system was observed in immature, ovariectomized, or mature female mice (Table 1). These observations were always made together with appropriate controls including aminopterin alone, estrogen or androgen alone, and the vehicles for the specific drugs employed. Marked genital enlargement was obtained following estrogen administration even when supralethal doses of aminopterin were employed

TABLE 1. EFFECT OF AMINOPTERIN ON THE ESTROGEN GROWTH RESPONSE OF THE FEMALE GENITAL TRACT IN THE MOUSE

Exp. No.	Aminopterin* mg./Kg.	Estrogen mg./Kg.	Folic acid mg./Kg.	Mean init. body wt. gm.	% Animal wt. change	Mean genital wt. mg. \pm S.E.	"p" \times estrogen-treated mice	CFI mice; I.P. inj.; single injection aminopterin; estrogen 1 day later. Experiment terminated on 4th day
1	5.0	—	—	11.2	-8.9	19.5 \pm 3.5	0.009	
a	5.0	10†	—	11.4	-12.3	59.5 \pm 6.2	0.73	
b	3.0	—	—	13.0	-11.5	24.4 \pm 2.8	0.055	
c	3.0	10	—	10.8	-9.3	53.8 \pm 9.5	0.52	
d	—	10	—	9.5	+16.8	64.9 \pm 13.1		
e	—	—	—	10.4	+10.4	32.0 \pm 4.5	0.044	
2A	0.3	—	—	15.3	-7.6	30.9 \pm 3.9	0.005	
a	—	10†	—	15.4	+9.1	149.6 \pm 25.1	0.34	
b	0.3	10	—	15.1	-9.9	118.0 \pm 17.9	0.0018	
c	—	—	—	15.6	+6.4	36.2 \pm 4.8		
2B	0.3	—	—	15.3	-7.6	30.9 \pm 3.9	<0.0009	
a	—	10†	—	15.1	+7.3	164.7 \pm 15.3		
b	—	10	—	14.8	-23.6	112.7 \pm 15.1	0.06	
c	0.3	—	—	15.4	+10.4	81.0 \pm 22.1	0.01	
d	—	—	—	15.3	-7.6	30.9 \pm 3.9	0.0014	
2C	0.3	—	—	14.6	+7.6	121.6 \pm 13.6	0.66	
a	—	10‡	—	15.4	-14.8	134.7 \pm 26.8	0.002	
b	0.3	10	—	14.9	+10.7	47.9 \pm 2.9		
3	0.3	—	—	19.2	+5.7	72.8 \pm 12.9	<0.0001	
a	—	5†	—	19.4	+7.4	195.2 \pm 10.9	0.054	
b	—	5	—	19.1	+2.6	160.3 \pm 10.6	0.001	
c	0.3	—	—	20.3	+8.1	97.4 \pm 17.0	<0.0001	
d	—	—	—	20.8	+3.6	53.9 \pm 5.8		
4	0.3	—	—	14.4	+0.4	23.4 \pm 2.8	<0.002	
a	—	10†	—	14.6	+1.3	96.8 \pm 7.7	0.14	
b	—	10	—	13.9	-0.6	72.9 \pm 12.3	<0.0001	
c	0.3	—	—	14.4	+1.9	34.4 \pm 4.6	0.0017	
d	—	—	—	14.1	+1.9	42.8 \pm 10.4		
5	0.3	—	—	14.1	+1.3	26.0 \pm 4.5	<0.0001	
a	—	10†	—	14.9	+1.3	162.4 \pm 12.3	0.88	
b	—	10	—	15.1	-5.4	159.5 \pm 11.6	0.0001	
c	0.3	—	—	15.5	+6.9	55.4 \pm 15.3	<0.0001	
d	—	—	—	15.8	+4.1	48.9 \pm 14.2	<0.0001	
6	0.3	—	—	8.8	-11.4	11.7 \pm 1.0	<0.0001	
a	0.2	—	—	7.9	+11.4	12.9 \pm 0.9	<0.0001	
b	—	10	—	8.3	+28.9	50.5 \pm 2.0	0.08	
c	—	10	—	8.7	+4.6	39.1 \pm 5.7	0.18	
d	0.2	—	—	8.4	+10.7	44.9 \pm 2.6	<0.0001	
e	—	—	—	8.6	+27.7	14.1 \pm 0.8	<0.0001	
f	—	—	—	8.3	+22.9	14.8 \pm 1.0	<0.0001	
g	—	—	—	8.3	+1.1	15.4 \pm 1.1	<0.0001	
h	—	—	—	8.6	-3.5	17.5 \pm 1.8	<0.0001	
i	—	—	—	8.1	+11.1	19.1 \pm 3.4	<0.0001	
j	—	—	—	8.1	+11.1	19.1 \pm 3.4	<0.0001	
7	0.3	—	—	19.5	-0.5	10.9 \pm 1.0	<0.0001	
a	—	0.00075	—	19.6	+8.7	38.9 \pm 3.8	0.95	
b	—	0.00075	—	18.9	+3.2	38.6 \pm 4.0	0.95	
c	0.3	0.00075	—	19.5	+6.2	39.3 \pm 5.0	0.25	
d	0.3	—	—	19.7	0	33.1 \pm 3.0	0.0002	
e	0.3	0.00075	—	19.5	+4.1	12.8 \pm 2.0	0.0001	
f	—	—	—	19.6	+5.6	12.8 \pm 1.2	0.0001	
g	—	—	—	19.6	+6.6	13.9 \pm 1.6	0.0002	
h	—	—	—	21.0	+3.3	28.1 \pm 5.1	0.1	

|| Estradiol dipropionate (Dimenformin Dipropionate), X-403114, Roche-Orion Inc.

† Crystalline α -estradiol, Schering Corp., Kenilworth, N.J., Lot No. 53106-3. Stated to be 90% pure.

‡ Estrogen in corn oil, Lot No. 526, Ayerst, McKenna and Harrison.

§ Stilbestrol.

¶ Uncastrated

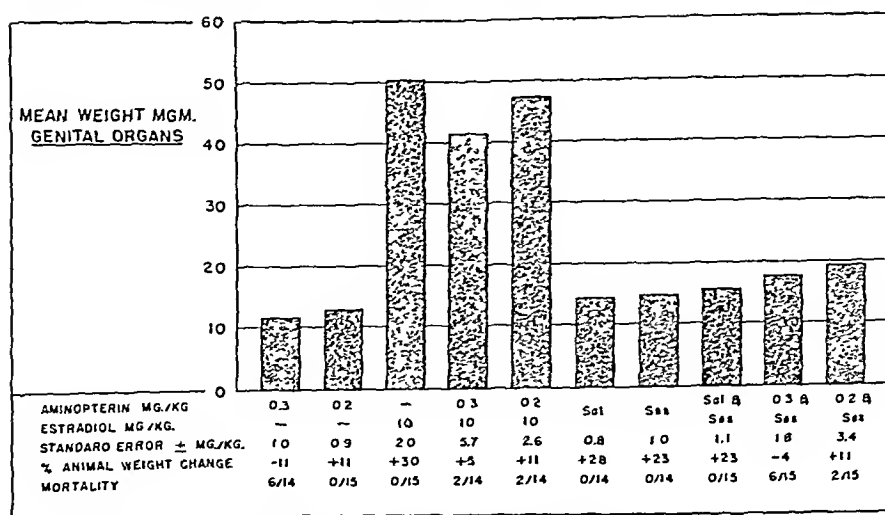


FIG. 1. Absence of aminopterin inhibition of the estrogen growth response in immature female mice. Aminopterin was administered on three successive days. Estrogen and sesame oil were administered on the second and third day. The experiment was terminated two days after the final injection. Sal=saline; Ses=sesame oil. In the last three groups, sesame oil was administered on the second and third day. All injections were made subcutaneously. (See Table 1, Experiment 6.) Dosages indicated are for single injections.

(Table 1, Experiment 1). Although a slight reduction in genital-tract weight was observed in mice treated with both the analogue and estrogen, this was also observed in animals receiving aminopterin alone. This slight reduction appeared to be correlated with the general impairment of growth that occurred after aminopterin administration. In no instance was this change deemed significant. The results of individual experiments in which immature and ovariectomized mice were employed are summarized in Figs. 1 and 2. It may be noted in Fig. 2 that folic acid was without stimulative effect on the genital tract when administered either alone, with aminopterin, or with aminopterin plus estradiol.

Testosterone, at the dosage employed in these experiments, induced a significant enlargement of the seminal vesicle (Fig. 3). This increase was slightly, but not significantly, reduced by the concomitant administration of aminopterin. Diminished gain in body weight was noted among mice

treated with aminopterin plus testosterone as compared with those treated with testosterone alone. In immature male mice, the administration of aminopterin plus estrogen produced no significant changes in seminal-vesicle weight as compared with the controls (Fig. 3).

DISCUSSION

In our experiments, the estrogen-induced growth response of the female genital tract and the androgenic growth stimulation of the seminal vesicle were not significantly depressed by administration of aminopterin in the mouse. Estrogen was administered both at massive physiological doses and at threshold doses. In those experiments in which minimal, but not significant, interference with stimulatory hormonal action occurred, less animal weight gain was noted in the mice treated with aminopterin plus hormone than in the mice treated with hormone alone. Mice treated with aminopterin

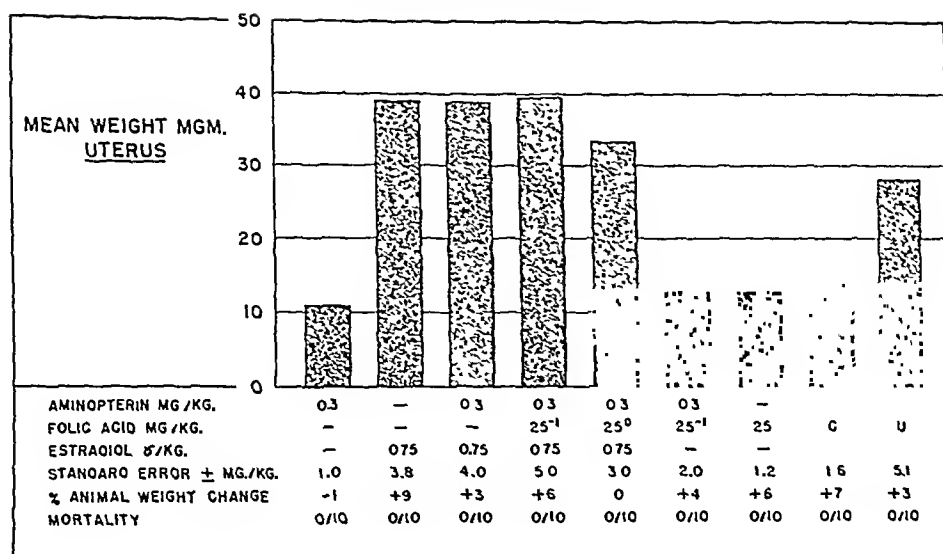


FIG. 2. Effect of aminopterin and folic acid on estrogen growth response in ovariectomized mice. The agents were administered on the following days: folic acid—day 1, 2, 3, 4; aminopterin—day 2, 3, 4; estrogen—day 3, 4, two injections daily. —1=folic acid administered one hour prior to aminopterin. 0 = folic acid and aminopterin administered concomitantly. C=control receiving n-saline on the days of aminopterin injection and 2 per cent sodium bicarbonate solution on the days of folic acid administration. Aminopterin and estradiol dissolved in n-saline. U = uncastrated control. Folic acid dissolved in 2 per cent sodium bicarbonate solution. Experiment terminated on the fifth day. (See Table 1, Experiment 7.) Dosages indicated are for single injections.

alone had, in general, somewhat smaller uteri, and failed to gain as much weight as controls receiving the vehicle alone. Thus, minimal reduction in weight of the genital tract following aminopterin administration appeared to parallel the general impairment of the growth of the animal.

Failure to obtain inhibition of the specific action of estrogen with the antifolic analogue cannot be attributed to administration of either insufficient antagonist or excess hormone. The amount of aminopterin employed in these studies included supra-lethal dosage and also repeated dosages approximating the maximum tolerated dose. Administration of aminopterin twenty-four hours prior to administration of estrogen permitted optimal prior action of the antagonist. The dosage of estrogen em-

ployed in one of the experiments (Table 1, Experiment 7) (0.75 γ per Kg. \times 4 of α -estradiol) was in the region of the minimal effective dose for the mouse, and is less on a per kilo basis than the amount employed by Hertz,⁸ or Brendler in studies on the rat. An optimal growth response to the administration of estrogen was obtained in each experiment.

The differential sex toxicity previously observed² was characterized by greater tolerance on the part of adult females to the lethal systemic toxicity of aminopterin when compared to adult males. The administration of estrogen to immature and mature males produced only a slight alteration in the sex difference.² Bilateral adrenalectomy was found to obliterate the sex difference completely. It was suggested that

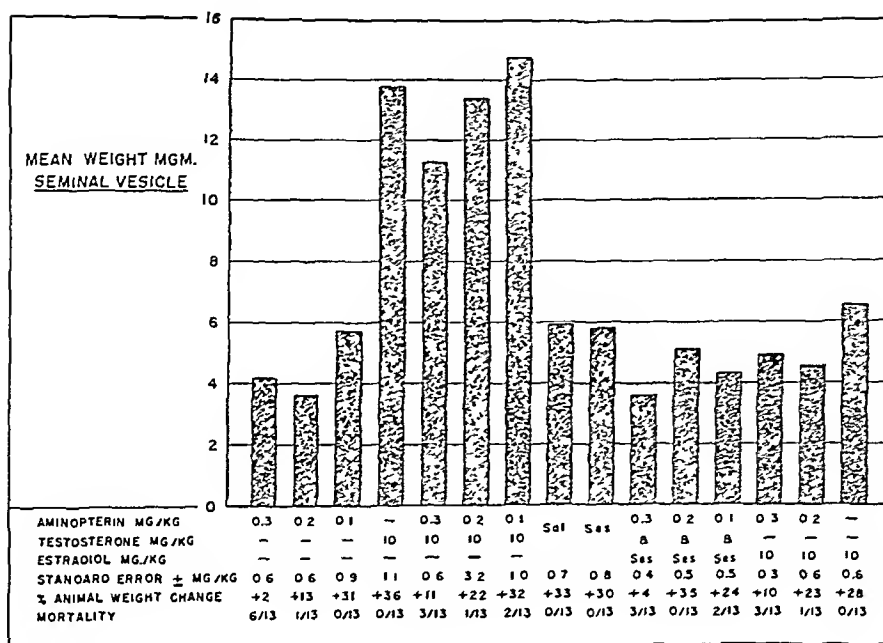


FIG. 3. Absence of aminopterin inhibition of testosterone growth response in immature male mice. Aminopterin was administered on three successive days. Testosterone and estradiol were administered on the second and third day. The experiment was terminated two days after the final injection. Sal = saline; Ses = sesame oil. All injections were made subcutaneously. CFV mice. Testosterone propionate (Perandren) Ciba No. 132834. Estradiol dipropionate (Ovocycin) Ciba No. 132520. Dosages indicated are for single injections.

the sex difference in lethal toxicity could be a reflection of differences in the metabolism of the adrenal steroids in females and in males.

In planning the experiments reported here, it seemed reasonable to expect a blockage of the physiological action of estrogens in mice, since a slight but apparently definite effect of estrogen was observed on the differential sex toxicity.² Furthermore, blockage of estrogen growth response had been reported in rats.⁸ However, the results of our experiments show no blocking effect of estrogen in mice. Since aminopterin has been demonstrated to be a potent antagonist of folic acid in mice,⁵ as well as in other species, it appears reasonable to conclude that the hormonally induced tissue-growth response in the mouse is essentially independent of the availability of folic acid.

This result is in contrast to previous reports of such a relationship in other animal species.

SUMMARY

In a series of experiments employing varying dosages and dosage schedules of aminopterin, folic acid, and estrogen, no significant alteration in the estrogen-induced growth response of the female genital system in mice was obtained with either aminopterin or folic acid.

Aminopterin did not significantly affect the seminal-vesicle enlargement induced by testosterone administration.

The lack of interference in estrogen-induced growth response by the antifolic analogue, aminopterin, is in contrast with observations reported in other animal species.

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STUDIES ON THE ROLE OF FOLIC ACID IN THE LEUKEMIC PROCESS

HOWARD E. SKIPPER, PH.D., JUANITA B. CHAPMAN, A.B.,
and MARTELIA BELL, B.S.

IT HAS been adequately demonstrated in both human and mouse leukemias that 4-amino-pteroylglutamic acid (aminopterin) and certain derivatives of this folic acid antagonist possess the ability to inhibit preferentially the production of leukemic white blood cells.^{3, 6, 12}

Burchenal et al.⁴ have recently reported that the antileukemic action of 4-amino-N¹⁰-methyl-pteroylglutamic acid can be blocked almost completely by prior administration of ten to twenty times as much folic acid.

The present investigation has involved a study of the effects of large doses of folic acid alone and in combination with aminopterin on the life span of mice with the rather acute transplanted Ak 4 strain leukemia. It appears quite evident that folic acid is a rate-controlling factor in this particular leukemia. An excess of folic acid speeds up the leukemic process, causing the animals to die before untreated controls. Administration of a compound (aminopterin) that antagonizes folic acid increases the life span of leukemic mice significantly, and thirdly, the antileukemic activity of a folic acid antagonist (aminopterin) can be reversed by administration of relatively large amounts of folic acid.

EXPERIMENTAL PROCEDURE

The antileukemic assay procedure employed has been described in a previous

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This investigation was supported by grants from Mr. Ben May, Mobile, Alabama; the American Cancer Society, on recommendation of the Committee on Growth of the National Research Council; and the Institute-Sponsored Research Fund, Southern Research Institute.

Received for publication, March 6, 1950.

publication.¹¹ Leukemia-susceptible Akm mice were inoculated with Ak 4 leukemia and treatment with aminopterin was begun after two days. Folic acid was injected intraperitoneally, beginning twenty-four hours after inoculation. The injection schedule was uniformly on an alternate-day basis for a total of ten injections, or for as long as the mice survived. The diet employed in these experiments consisted of Purina laboratory chow supplemented with bread and milk and raw carrots.

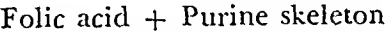
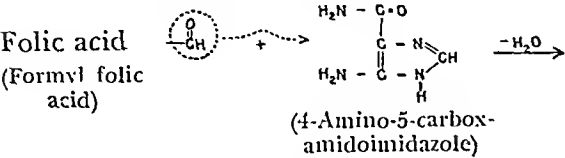
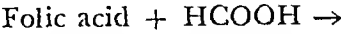
RESULTS

The results of the three separate experiments with individual control groups are self-consistent. The summarized data are given in Table 1. The internal consistency of the experiments is indicated in the simple statistical analysis. From the statistical point of view, there is less than one chance in a hundred that the observed accelerating effect of folic acid on the leukemic process might be anomalous.

DISCUSSION

Woolley and Pringle have recently noted the formation of 4-amino-5-carboxamidoimidazole during growth of *Escherichia coli* in the presence of 4-amino-pteroylglutamic acid. This possible purine precursor, first observed to accumulate during sulfonamide bacteriostasis by Stetten and Fox and later identified by Shive et al., offers interesting possibilities as a basis for the biochemical explanation of the present results and those of Burchenal.⁴ Gordon et al. have suggested that formyl folic acid is a functional derivative of folic acid, perhaps being involved in the introduction of the single carbon unit into purines and pyrimidines. Sonne, Buchanan, and Delluva

have injected isotopic formate into pigeons and observed that 72 per cent of the ureide carbon of the newly formed uric acid was derived from the administered formate. If, as Woolley suggests, aminopterin leads to a folic acid deficiency, which in turn is responsible for a failure in purine synthesis, then it would appear that the rate-controlling function of folic acid in leukemia might be found in the last step of biosynthesis of the purine skeleton, that step being the transfer of formate via formyl folic acid to the 2-position of the purine skeleton.



(In view of the observation of Getler et al. that free hypoxanthine is not a precursor of nucleic acid purines, it would appear that either some derivative of 4-amino-5-carboxamidoimidazole or hypoxanthine, possibly the ribosides of these compounds, might act as purine precursors.)

N¹⁰-Methylpteroylglutamic acid,⁵ N¹⁰-phenacylpteroylglutamic acid,⁵ and 9,N¹⁰-dimethylpteroylglutamic acid⁸ are three examples of the complete loss of growth-promoting activity of the basic folic acid structure that accompanies blocking of the N¹⁰ group.

It has been reported by Bethell et al. that the folic acid content of human leukemic

TABLE 1
ANTILEUKEMIC ASSAY DATA

Exper. no.	Dose (mg./Kg.)		No. mice	Survival time (days)		
	Folic acid	Aminopterin		Range	Mean	S.D.*
1	—	—	10	7-14	8.8	2.2
	60	—	10	7-8	7.2	0.4
	—	0.23	10	14-20	16.8	2.2
	—	0.18	10	14-19	15.7	1.7
	—	0.12	10	10-17	13.9	1.6
	—	0.06	10	8-13	9.8	1.3
2	60	0.23	10	13-16	14.0	1.1
	—	—	10	7-10	8.4	1.2
	60	—	10	7-8	7.5	0.5
3	—	0.23	10	12-18	15.7	1.6
	—	—	10	7-12	10.2	1.6
	60	—	10	8-9	8.1	0.3
	—	0.23	20	10-17	14.0	2.0
	60	0.23	10	8-13	11.0	1.3

* Standard deviation

leukocytes is much higher than that of normal leukocytes. If the requirement of purines, purine nucleosides, and purine nucleotides (for formation of cellular nucleoproteins) is greater in the more dynamic leukemic cell-forming tissue than in normal cells, then an excess of folic acid might be expected to speed up the leukemic process and a deficiency might preferentially depress malignant mitosis. Such results have been obtained in the present experiments.

This theory is, of course, not original, but if it can be further substantiated (tracer experiments with this objective are under way in this laboratory), a clearer understanding of the biochemical mechanism of action of a known type of antileukemic agent might be forthcoming.

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INTERFERENCE BETWEEN CERTAIN NEUROTROPIC VIRUSES AND TRANSPLANTABLE MOUSE TUMORS

HILARY KOPROWSKI, M.D., and THOMAS W. NORTON

THE concept of parasitizing tumor tissue to control neoplastic processes in experimental animals that has occupied many investigators in the past was briefly reviewed by Moore¹ in a recent publication. Following the report of Levaditi and Nicolau, in 1923, that high concentrations of vaccinia virus were observed in epitheliomas of mice and rats, other workers have demonstrated that various other viruses show affinity for transplantable experimental tumors. Moreover, in a few cases, a definite interference with the actual growth has taken place. For instance, Levaditi and Haber reported, in 1937, that the avian pest virus caused necrosis of an epithelial mouse tumor, and bioassays made with the remnants of the tumor indicated that the cells were no longer viable. In 1947, infection of sarcoma 180 with neurovaccinia virus was shown by Turner and Mulliken not only to affect the rate of growth of the tumor but also to render the tumor cells nonviable, as judged by failure to obtain further transplants. Recently, Moore³ reported that the Russian spring-summer-

encephalitis virus parasitized mouse sarcoma 180, inhibited its growth, and caused extensive cellular damage, as evidenced by the complete inability to secure transplants by grafting virus-bearing tumor fragments into mice.

The present study was undertaken to determine what other neurotropic viruses might possibly have oncolytic properties.

MATERIALS AND METHODS

Viruses. The following viruses were tested: French neurotropic strain of yellow fever; Bwamba Fever (M483 strain); Ntaya; Passos I; pseudorabies; St. Louis encephalitis (Brown strain); Ilhéus encephalitis; Semliki Forest; Bunyamwera; West Nile (M956 strain); Japanese B encephalitis (Nakayama strain); louping-ill; western, eastern, and Venezuelan equine encephalomyelitis; and Russian spring-summer encephalitis.

The viral inocula were of mouse-brain origin in the form of 40 per cent suspensions in distilled water kept in a frozen state in a CO₂ box. Inoculations into tumor-bearing mice were done by parenteral, that is, either intra-abdominal or subcutaneous, routes. In all instances except for three viruses (Russian spring-summer, Semliki Forest, and Venezuelan), each tumor-bearing mouse was inoculated with 0.5 ml. of 40 per cent mouse-brain suspension infected with the respective viruses. In the case of Russian spring-summer and Semliki Forest viruses, 10⁻³ dilution of infected mouse brain was inoculated in 0.2 ml. amounts, either by intra-abdominal or subcutaneous routes, whereas with the Venezuelan virus, the inocula varied as stated in each protocol.

Tumors. The following transplantable mouse tumors were used: Crocker sarcoma

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The viruses of Russian spring-summer encephalitis and louping-ill were obtained through the courtesy of Dr. Peter K. Olitsky of The Rockefeller Institute for Medical Research; the viruses of Bunyamwera, Bwamba Fever, Ntaya, Passos I, and Semliki Forest were received through the kindness of Dr. Kenneth C. Smithburn of The Rockefeller Foundation, New York.

The six tumors used were obtained through the kindness of Dr. Alice E. Moore, Memorial Center for Cancer and Allied Diseases, New York, New York. The authors are indebted to Dr. C. P. Rhoads, Director of the Center, and to Dr. Moore for their most helpful collaboration, and particularly for their personal communications stimulating our interest in the study of virus-tumor interference prior to the publication of Dr. Moore's results.

The authors wish to thank Mrs. Doris Nelsen and Mrs. Priscilla Roberts for their valuable technical assistance, and Miss Maja Platzter for her invaluable aid in the preparation of the manuscript.

Received for publication, March 22, 1950.

180 (Swiss albino mice), Patterson mouse lymphosarcoma (Akm mice), Wagner mouse osteogenic sarcoma (Akm mice), Ridgeway mouse osteogenic sarcoma (Akm mice), mouse mammary adenocarcinoma EO 771 (C57 black mice), and methylcholanthrene-induced sarcoma (Swiss albino mice).

Mice. The Akm strain of mice was purchased from Carworth Farms, from a stock bred for the Sloan-Kettering Institute for Cancer Research; the C57 black mice were purchased from Rockland Farms, and the Swiss albino mice from Tumblebrook Farms. The Akm and C57 black mice weighed 18 to 22 gm. each. The Swiss albino mice were of the same weight in some of the experiments, but in some of the tests, mice 10 to 12 gm. in weight were used because of the greater susceptibility of younger mice to parenteral virus inoculations.

Techniques. More of the studies were done with sarcoma 180 because of the greater availability of the Swiss strain of mice and because of the relative ease with which the tumor may be cultivated. The technique followed closely that of Moore³ and will be described only briefly.

The tumor was grown in the subcutaneous tissue of albino Swiss mice for seven days; the mass was then removed, cut into 2-mm. cubes, and one cube per mouse implanted by use of trocar into the subcutaneous tissue of the pectoral muscles. Four days after the transplantation, all mice bearing palpable tumors were culled, in general separated into groups of six mice each, and inoculated with the respective viruses. Five days later, the tumors of the virus-infected mice were measured with calipers in two diameters and the tumor outlines were recorded. At this time, also, the tumors of the same age in the untreated controls were measured and recorded for comparative purposes. After the virus-inoculated mice showed signs of illness, the animals were sacrificed, and the tumor tissue, if any, removed, cut into 2-mm. cubes, and

implanted subcutaneously in mice. Whenever possible, transplants of tumors were made from one virus-infected mouse into five or six other mice. This technique was applied also to the other tumors, except that the virus inoculations were given at longer than four-day intervals after transplantation because of the rather delayed and irregular growth rate of the tumors.

In many instances, only one half of the presumably infected tumor was used for bioassay. The remaining half, combined with other fragments of similar tissues, was made into a 10 per cent suspension in physiological salt solution and centrifuged for five minutes at 1500 r.p.m. Tenfold serial dilutions of the supernate in physiological salt solution were injected into Swiss mice in 0.03 ml. amounts by the intracerebral route. In some instances, tumor-bearing, virus-infected mice were bled from the heart, their blood samples pooled, and the serum separated and titrated in mice. Also, in several instances, brain tissue was removed from the carcasses, and a 10 per cent suspension was prepared and titrated in mice. All animals were observed daily, and the number of sick and dead was recorded.

Presentation of Results. In general, only those experiments are discussed in this report in which all of the tumor-implanted, virus-inoculated mice became sick or moribund. The few instances in which the infectivity ratio was less than 100 per cent are recorded in the tables.

The results of bioassays are given in terms of ratios of mice that developed tumors after implantation with presumably virus-infected fragments of the respective tumors, and of controls that received transplants of tumors from mice that had not been given viral treatment. The growth of tumors was determined on several occasions, but the records presented in the tables give results observed at the time most unfavorable to the group that received transplants from virus-infected mice, and the size of these tumors, if any, was com-

pared to the control tumors of the same age. A number of tracings of the original tumors and of their respective transplants are reproduced to illustrate the general trend of experimental results.

EXPERIMENTAL RESULTS

Crocker Sarcoma 180. EFFECT OF RUSSIAN SPRING-SUMMER AND WEST NILE VIRUSES. It may be observed in Table 1 that the single experiment in which Russian spring-summer virus was used confirmed its interfering action as described by Moore.³

West Nile virus introduced into mice bearing four-day-old sarcoma 180 caused frank signs of illness, usually on the fourth or fifth day after inoculation. The tumors in the virus-infected mice did not reveal any great differences in size, although, in general, the virus-infected tumors were slightly smaller than those in the noninfected controls. However, the results of bioassay, as indicated in Table 1, showed a definite interfering effect of the West Nile infection. In the first three experiments (A, B, and C), the virus-infected tumor

TABLE 1
INTERFERING EFFECT OF CERTAIN NEUROTROPIC VIRUSES ON THE
VIABILITY OF MOUSE SARCOMA 180

Virus strain	Exp.	LD ₅₀ virus titer in:			Results of bioassay; transplants originating from:		
		Tumor tissue	Brain tissue	Blood	Virus-inoculated mice	Noninfected controls	
					Ratio of tumor-bearing mice*	Size of tumors†	Ratio of tumor-bearing mice*
West Nile	A	10 ^{-3.00}			2:5	Smaller	5:5
	B	10 ^{-2.00}			3:6	Smaller	6:6
	C	10 ^{-2.00}			3:6	Smaller	6:6
	D	10 ^{-3.50}	10 ^{-3.50}	<undil.	6:21	Smaller	10:10
	E	10 ^{-3.10}	10 ^{-4.00}	<undil.	3:16	Smaller	10:10
	F	10 ^{-3.00}			1:4	Smaller	5:5
	G	10 ^{-3.00}	10 ^{-4.00}	<undil.	0:5	No growth	6:6
	H	†			0:5	No growth	5:5
Ilhéus	I	10 ^{-3.50}			4:5	Smaller	8:8
		10 ^{-3.50}			0:5	No growth	5:5
		10 ^{-4.75}	10 ^{-3.50}		0:5	No growth	5:6
St. Louis		>10 ^{-5.00}			0:4	No growth	5:5
		10 ^{-4.50}			1:5	Smaller	5:5
		10 ^{-3.50}	10 ^{-4.50}		1:5	Smaller	5:5
Louping-ill		†			0:5	No growth	5:5
		†			0:5	No growth	5:5
		10 ^{-5.50}			0:5	No growth	5:5
		10 ^{-5.95}			0:5	No growth	5:5
Russian spring-summer		>10 ^{-1.00}			0:6	No growth	6:6
Bunyamwera		10 ^{-2.50}			4:4	Same	5:5
		10 ^{-2.50}			5:5	Same	5:5
Semliki Forest		10 ^{-4.25¶}			4:4	Same	3:5
		10 ^{-3.00}			3:3	Same	8:8
		10 ^{-5.00}			5:5	Same	6:6
Japanese B		10 ^{-2.50}			5:5	Smaller	5:5
		10 ^{-3.75}			5:5	Same	5:5
Eastern equine encephalitis		<10 ^{-1.00}			5:5	Same	5:5
		<10 ^{-1.00}			5:5	Same	5:5
		<10 ^{-1.00}			5:5	Same	4:5

* Antecedent = number of mice with measurable tumors; consequent = number of mice implanted with tumor cubes.

† Compared on the same day after transplantation with tumors originating from noninfected control mice.

‡ Not tested.

¶ Titer of virus in brain tis. $\geq 10^{-6.50}$.

|| Infectivity ratio 3:6.

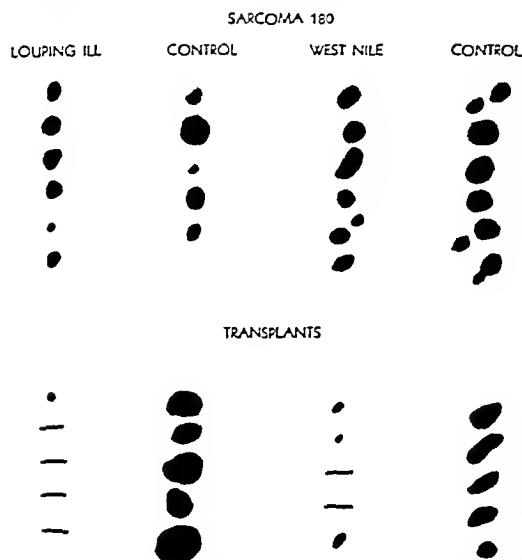


FIG. 1. Effect of louping-ill and West Nile viruses on sarcoma 180.

cubes apparently contained only enough viable cells to cause growth of another tumor in about one half of the animals. In subsequent experiments, the ratio of tumors from virus-inoculated mice was still smaller, and in two experiments (G and H), no tumors grew from transplants of virus-infected fragments. This interpretation appears to be substantiated by experiments D and E, in which the virus-infected tumors were transplanted into a greater number of mice, but tumors grew in only six of twenty-one, and in three of sixteen mice, respectively.

Tumors resulting from transplants of virus-infected fragments grew also at a much slower rate. Thus, the weight of tumors in experiments C and D was 0.11 gm. each when weighed on the eleventh day after transplantation, whereas the weight of a tumor from a noninfected transplant, measured at the same time after transplantation, was 0.79 gm., about seven times heavier. It should be pointed out that, in all instances, the results of bioassay from noninfected tumors gave 100 per cent results.

West Nile virus was found in all the tumor tissues, the LD₅₀ titers ranging from 10^{-2.00} to 10^{-3.60}, but that this was not due

simply to its possible presence in the blood was demonstrated by experiments D, E, and G, in which the virus was not recovered from the blood pool of the virus-infected mice, and the titer in brain tissue was only about 1 log higher than in the tumor tissue.

EFFECT OF ILHÉUS, ST. LOUIS ENCEPHALITIS, AND LOUPING-ILL VIRUSES. The results in experiments with the Ilhéus and St. Louis encephalitis viruses seem to parallel those with the West Nile virus, with the exception of experiment I, in which the interfering effect of viral infection, if present at all, was negligible. Again, the viral agents were present in the neoplastic tissues, and, in those animals that were tested, comparable LD₅₀ titers were obtained from the brain tissues. The results of the four experiments in which the louping-ill virus was used as infecting agent indicate that, in all cases, viral infection rendered the five virus-infected tumor fragments used for transplantation incapable of further self-propagation. In contrast, tumor fragments obtained from noninfected controls gave rise in every instance to new tumors.

The results of these experiments are also depicted in Figs. 1 and 2, in which

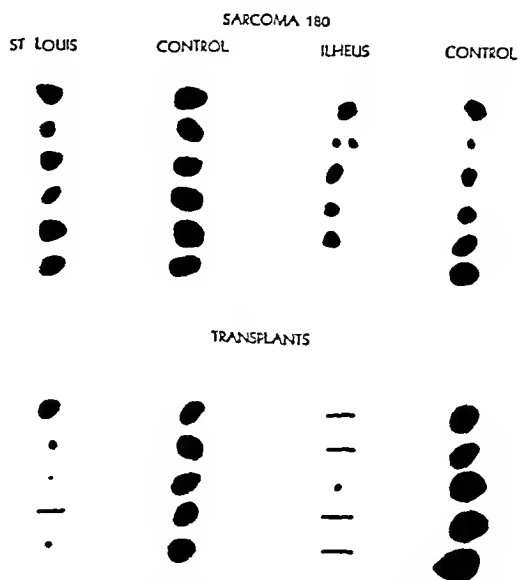


FIG. 2. Effect of St. Louis and Ilhéus encephalitis viruses on sarcoma 180.

representative experiments were chosen to show the characteristic behavior of tumor tissues affected by these viral agents. It may be observed that the viral infection had no apparent effect on the original tumors (upper half of each figure), but the size of the tumors obtained from virus-infected transplants seems to demonstrate clearly the interfering action of the viruses. The tumor in the loup-ill transplant never grew beyond the pin-point size, and no trace of tumor tissue was found in the same animal five days later. Three of the transplants from West Nile-infected tumors finally gave rise to small tumors, but one regressed completely, as did the loup-ill and Ilhéus transplants. From the transplants of St. Louis-infected tumors, only one of the five gave rise to a tumor that ultimately grew to a size equal to that of the control.

EFFECT OF BUNYAMWERA, SEMLIKI FOREST, JAPANESE B ENCEPHALITIS, AND EASTERN EQUINE-ENCEPHALITIS VIRUSES. It is interesting to note that when Bunyamwera, Semliki Forest, and Japanese B encephali-

tis viruses were used (Table 1), the infecting agent was always recovered from the neoplastic tissue, and, in some instances (Semliki Forest), in quite a high concentration. However, in not a single instance did these viruses interfere with the viability of the tumor cells, as evidenced by the results of the bioassays. Conversely, in Eastern equine-encephalitis-virus infection, a 10 per cent suspension of tumor tissue obtained from a moribund mouse failed to elicit signs of infection in intracerebrally inoculated mice in three consecutive experiments. The same virus also failed to interfere with the viability of the tumor. The fact that the Eastern equine-encephalitis virus produced signs of fulminant sickness in the inoculated mice without affecting the viability of the tumor tissue indicates that severity of illness in itself is not the dominant factor responsible for the interference observed with the other viruses (Table 1).

EFFECT OF FRENCH NEUROTROPIC STRAIN OF YELLOW-FEVER, NTAYA, PASSOS I, PSEUDORABIES, BWAMBA FEVER, AND WESTERN EQUINE-ENCEPHALITIS VIRUSES. Tumor-

TABLE 2

INTERFERING EFFECT OF VENEZUELAN EQUINE-ENCEPHALOMYELITIS VIRUS
ON THE VIABILITY OF MOUSE SARCOMA 180

Exp.	Tumor-bearing mice inoculated with:		LD ₅₀ virus titer in tumor tissue	Results of bioassay; transplants originating from:		
	Virus dilutions	Route		Virus-inoculated mice	Noninfected controls	
				Ratio of tumor-bearing mice*	Size of tumors†	Ratio of tumor-bearing mice*
A	10 ^{-3.00}	Subcut.	>10 ^{-6.60}	4:4	Same	4:4
B	10 ^{-5.00}	Subcut.	10 ^{-5.20}	2:3	Smaller	4:4
C	10 ^{-4.00}	Subcut.	10 ^{-5.70}	4:4	Smaller	4:4
D	10 ^{-4.00}	Subcut.	10 ^{-4.70}	0:6	No growth	5:5
E	10 ^{-5.00}	Subcut.	10 ^{-4.60}	0:3	No growth	4:4
F	10 ^{-5.00}	Subcut.	10 ^{-5.70}	0:4	No growth	4:4
G	10 ^{-3.00}	Subcut.	10 ^{-4.25}	5:5¶	Same	5:5
			10 ^{-4.25}	0:5	No growth	5:5
H	10 ⁻¹	Subcut.	10 ^{-5.70}	2:4	Smaller	8:8
	10 ⁻²	Subcut.	†	0:4	No growth	
	10 ⁻⁴	Subcut.	10 ^{-5.50}	1:4	Smaller	
	10 ⁻⁵	Subcut.	10 ^{-5.25}	4:4	Smaller	
	10 ⁻⁶	Subcut.	<10 ^{-1.00}	4:4	Same	
I	Feeding: One infected mouse brain per mouse		10 ^{-3.70}	0:4	No growth	4:4
			>10 ^{-5.00} §	2:4	Same	4:4
			10 ^{-4.50}	4:4	Same	4:4

* Antecedent = number of mice with measurable tumors; consequent = number of mice transplanted with tumor cubes.

† Compared on the same day after transplantation with tumors originating from noninfected control mice.

‡ Not tested.

¶ Mice immune to Venezuelan virus.

|| Nonimmune mice.

§ LD₅₀ titer of brain tissue, 10^{-9.00}; of blood, 10^{-7.75}.

bearing mice inoculated with these viruses, respectively, only occasionally and irregularly became infected by the parenteral route, and the infectivity ratio was rarely higher than 1:6 or 2:6. The tumors in the virus-infected mice showed no appreciable difference from those in the noninfected controls, and subsequent transplants gave rise to tumors that grew at the same rate and reached the same size as that obtained by transplants from nonviral treated controls.

EFFECT OF VENEZUELAN VIRUS. Inoculation of Venezuelan virus into mice bearing sarcoma 180 was invariably followed by illness on the fifth day after inoculation, and in many instances the infection curbed the growth of the original tumors to a degree comparable to that described by Moore³ with the Russian spring-summer virus. However, when these small shrunk tumors were transplanted into Venezuelan-immune mice, the transplants grew at a rate comparable to that of untreated controls in some instances (Table 2, A); in

some instances, no growth of tumor occurred after transplantation (D, E, and F); whereas in others, although growth was observed, the terminal size of the transplanted tumor was much smaller than that of the untreated controls (B and C). The use of Venezuelan-immune mice is necessary, inasmuch as in earlier experiments it had been observed that transplantation of virus-containing tumor fragments into normal mice resulted invariably in the death of the animal owing to infection with the Venezuelan virus. To investigate whether or not the erratic behavior resulted from the use of Venezuelan-immune mice, fragments from the same virus-infected tumor were transplanted both into Venezuelan-immune mice and into normal mice (experiment G). As indicated in Table 2, transplants into the Venezuelan-immune mice resulted in tumor growth in all of the inoculated mice, but in the nonimmune mice, which became moribund on the sixth day after transplantation, no trace of tumor tissue was found; whereas, in the controls that received transplants from noninfected control mice, tumors had grown to sizeable proportions by that time.

In experiment H are summarized results of an attempt to determine whether or not any relationship exists between the dilution of virus used in the inoculum and the oncolytic effect. This appeared to be possible, since the tumor growth was curbed to the highest degree in those mice that received the lowest dilution of infected mouse-brain suspension (to such a degree that there was not enough tumor tissue left in mice infected with the 10^{-2} dilution for titration purposes). However, as is evident from the bioassays, results were far from uniform and were inconclusive in character. Tracings of tumors obtained from mice infected with 10^{-2} and 10^{-5} dilution respectively, as well as of the respective transplants secured from such tumors, are shown in Fig. 3. Comparing these with the untreated controls, it may be observed that in all instances the tumors in the virus-treated mice were of smaller size than in

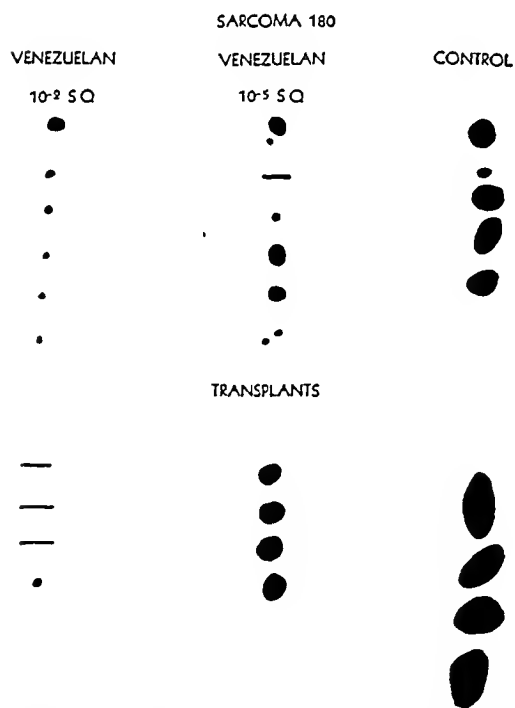


FIG. 3. Effect of Venezuelan equine-encephalomyelitis virus on sarcoma 180.

the controls, though the difference was more marked in mice inoculated with 10^{-2} dilution than with the 10^{-5} dilution. In one case, the transplants did not give rise to tumors; in the other (10^{-5} dilution), the interfering action of the virus was only presumptive because of the slower rate of growth of the virus-infected tumor implants, as compared to the controls.

In order to test the possibility that the route of introduction of the virus may have an effect on the results, mice bearing three-day-old sarcoma 180 were starved for twenty-four hours and then placed in individual cages, and each was given as food one Venezuelan-infected mouse brain (Table 2, I). First signs of sickness were usually noted on the sixth day after the infectious meal, at which time the mice were sacrificed. It was found that the tumor growth had been curbed markedly, as compared to control noninfected tumors, and yet the results of the bioassays were as irregular as in the previous experiments.

That the virus seemed to concentrate in the tumor tissue is indicated by the high LD_{50} titers in mice (Table 2). It may be added at this point that, in contrast to the West Nile virus, infection with Venezuelan

virus in mice was accompanied by viremia and yet the titer of the virus in the blood never exceeded $10^{-3.75}$, about 2 logs lower than the titer of the virus in tumor tissue. Again, there seems to be no doubt that an affinity between Venezuelan virus and tumor tissue does exist.

Encouraged by the results obtained with the West Nile virus, and not exactly encouraged but rather puzzled by the behavior of the Venezuelan virus, we extended the studies to tumors other than sarcoma 180.

Methylcholanthrene Sarcoma, Adenocarcinoma EO 771, Wagner Osteogenic Sarcoma, and Ridgeway Osteogenic Sarcoma. EFFECT OF WEST NILE VIRUS. It may be seen in Table 3 that West Nile virus showed marked interfering activity with tumor growth in the case of methylcholanthrene-induced sarcoma. Even in experiment A, in which two of five implants had enough viability to start growing, the resulting tumors were of much smaller size than the tumors obtained from implants of noninfected controls. Moreover, in every instance, the LD_{50} titer of the virus in tumor tissue was high, indicating again the

TABLE 3

INTERFERING EFFECT OF WEST NILE VIRUS ON THE VIABILITY OF TRANSPLANTABLE MOUSE TUMORS OTHER THAN SARCOMA 180

Exp.	Tumor type	Virus inoculated after tumor implant days	LD_{50} virus titer in tumor tissue	Results of bioassay; transplants originating from:		
				Virus-inoculated mice		Noninfected controls
				Ratio of tumor-bearing mice*	Size of tumors†	Ratio of tumor-bearing mice*
A	Methylcholanthrene-induced sarcoma	6	$10^{-4.00}$	2:5	Smaller	4:5
B		7	$>10^{-3.00}$	0:4	No growth	5:5
C		7	$10^{-4.50}$	0:6	No growth	5:6
D		7	$10^{-5.90}$	0:5	No growth	5:5
E	Adenocarcinoma EO 771	7	$10^{-1.70}$	0:5	No growth	4:5
F		7	$10^{-4.50}$	0:5	No growth	3:4
G		7	$10^{-3.50}$	6:6	Smaller	6:6
H		12	$10^{-3.90}$	6:6	Same	5:5
I	Wagner osteogenic sarcoma	14	$10^{-5.00}$	0:5	No growth	5:5
J		14	$>10^{-5.00}$	0:6	No growth	5:5
K	Ridgeway osteogenic sarcoma	22	$10^{-1.70}$	0:5	No growth	5:5
L		15	$10^{-5.50}$	0:5	No growth	5:5
M		22	$10^{-5.50}$	0:5	No growth	4:4

* Antecedent = number of mice with measurable tumors; consequent = number of mice implanted with tumor cubes.
† Compared on the same day after transplantation with tumors originating from noninfected control mice.

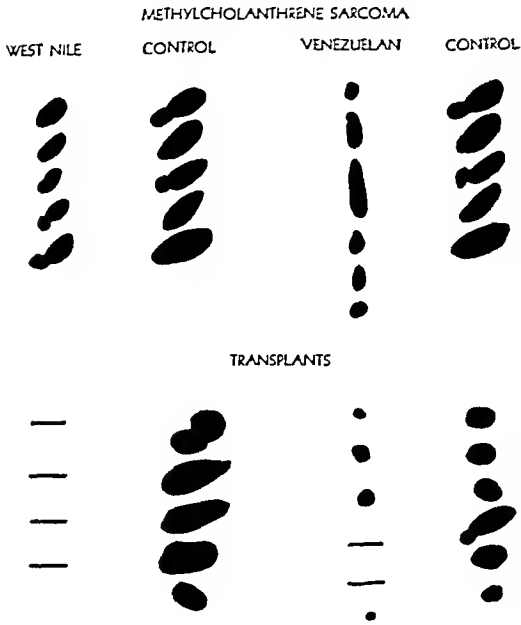


FIG. 4. Effect of West Nile and Venezuelan equine-encephalomyelitis viruses on methylcholanthrene-induced sarcoma.

affinity of the pathogen for tumor tissue. The results of experiment B, presented in Fig. 4, indicate that, although the original tumors infected with West Nile virus seemed to be only slightly smaller than the corresponding controls, no tumor grew from the transplanted virus-infected tissue, in contrast to the nonviral tumor tissue that gave rise to large tumors.

In experiments with adenocarcinoma EO 771, results of bioassay in experiments E and F (Table 3) seem to indicate that West Nile virus interfered with the oncotic process. Graphic presentation of experiment E is shown in Fig. 5. The transplants remained the size of pin points and seemed to undergo complete absorption within four days after the measurements were taken. Conversely, results of the two other experiments (G and H), in which good titers were obtained in tumor tissue, indicated a general failure of the virus to interfere, although in experiment G, the tumors that resulted from virus-infected implants seemed to be of smaller size than the nonviral control tumors.

If one may draw any conclusions from

five experiments, West Nile virus seemed to display definite interfering effect in the case of the Wagner and Ridgeway osteogenic sarcomas (Table 3). This is not only evidenced by the complete failure to obtain tumors from virus-infected transplants, but also by the fact that, in every instance, inoculation of West Nile virus seemed to arrest markedly the development of the original tumor. It may be also of interest to note that, in experiments L and M, fragments from the identical Ridgeway tumor were used but the interval for virus inoculation varied and yet the end results were the same, since on bioassay, the virus-infected tissue failed to grow.

EFFECT OF VENEZUELAN VIRUS. The effect of Venezuelan virus on the Ridgeway and Wagner osteogenic sarcomas (Table 4) was even more marked than that of the West Nile virus, since not only was the growth of tumors in the infected mice arrested but also marked shrinkage in size occurred. As indicated in Table 4, the virus was present in tumor tissue, and the results of the bioassays confirmed the impression

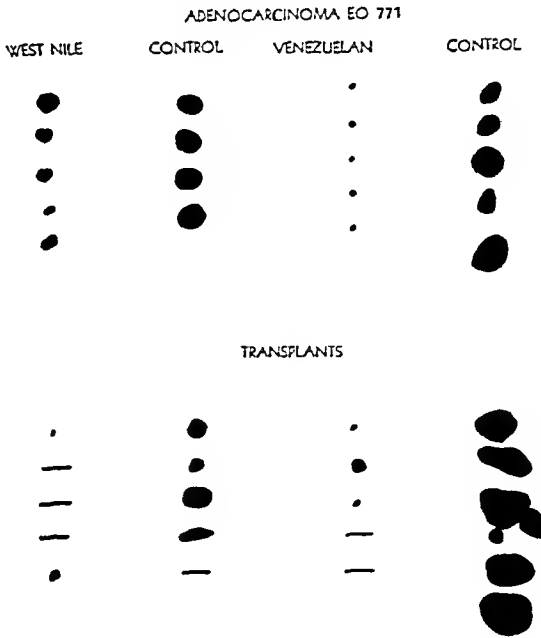


FIG. 5. Effect of West Nile and Venezuelan equine-encephalomyelitis viruses on adenocarcinoma EO 771.

gained that the Venezuelan virus interfered markedly with the viability of the tumor tissue.

The results of bioassays of methylcholanthrene-induced sarcoma and adenocarcinoma EO 771 originating from mice infected with Venezuelan virus were less encouraging (Table 4), despite the fact that the virus seemed to parasitize the tumor tissue quite heavily. The effect of the virus on the original tumor implants was quite marked, as indicated in Figs. 4 and 5, particularly in case of adenocarcinoma EO 771 (Fig. 5). Yet, on bioassays, three of the methylcholanthrene tumor transplants (Table 4, B) and one of the adenocarcinoma EO 771 implants (D) finally gave rise to tumors, but after a much slower rate of growth than of the control tumors.

EFFECT OF JAPANESE B ENCEPHALITIS, SEMLIKI FOREST, BUNYAMWEA, ILHÉUS, LOUPING-ILL, ST. LOUIS ENCEPHALITIS, AND EASTERN EQUINE-ENCEPHALITIS VIRUSES. The effect of these viruses upon the viability of the tumors is summarized in Table 5. It may be observed that in the methylcholanthrene-sarcoma group, infection of mice with Japanese B, Semliki Forest, and Bunyamwea viruses seemed to have little, if any, effect, since neither was the size of the original tumors influenced by the in-

fections nor did the results of bioassays bring out any conclusive differences. In contrast to these viruses, louping-ill, St. Louis, and Ilhéus viruses seemed to interfere with the viability of the methylcholanthrene sarcoma, if one may judge on the basis of results in single experiments. In all these experiments, the LD₅₀ titers indicated that the pathogens were present in the neoplastic tissues, and in the case of Japanese B virus in quite a high concentration.

In the adenocarcinoma EO 771 group, Japanese B, Semliki Forest, and Bunyamwea viruses failed to exert any influence on the viability of the tumor cells, as indicated by negative results of the bioassays, despite the high titers of the viruses in tumor tissues. The three implants obtained from Bunyamwea-virus-infected tumor tissue showed a slower growth rate than the control material, yet finally tumors grew in all three mice. Louping-ill and St. Louis encephalitis viruses seemed to interfere with the viability of the cells, as did Ilhéus virus in one experiment. In the second experiment with Ilhéus virus, results were negative; they may have been influenced by the more prolonged period between tumor implantation and virus inoculation. However, virus was present in tumor tissues in both

TABLE 4

INTERFERING EFFECT OF VENEZUELAN EQUINE-ENCEPHALOMYELITIS VIRUS ON THE VIABILITY OF TRANSPLANTABLE MOUSE TUMORS OTHER THAN SARCOMA 180

Exp	Tumor type	Virus inoculated after tumor implant days	LD ₅₀ virus titer in tumor tissue	Results of bioassay; transplants originating from*		
				Virus-inoculated mice		Noninfected controls
				Ratio of tumor-bearing mice*	Size of tumors†	Ratio of tumor-bearing mice*
A	Methylcholanthrene induced sarcoma	7	10 ^{-5.75}	2:3	Same	3:6
B		6	10 ^{-5.25}	3:6	Smaller	6:6
C	Adenocarcinoma EO 771	7	>10 ^{-6.50}	4:4	Same	5:5
D		7	†	1:5	Smaller	5:5
E		7	10 ^{-6.00}	4:6	Smaller	5:5
F	Wagner osteogenic sarcoma	14	10 ^{-5.50}	0:5	No growth	6:6
G	Ridgeway osteogenic sarcoma	11	†	0:4	No growth	5:5
H		22	10 ^{-6.45}	0:5	No growth	5:5

* Antecedent = number of mice with measurable tumors, consequent = number of mice implanted with tumor cubes

† Compared on the same day after transplantation with tumors originating from noninfected control mice

‡ Not tested

instances and even in much higher concentration in the second experiment.

The results with the Wagner and Ridgeway osteogenic sarcomas are of some interest, since the Bunyamwera virus seemed to interfere with the viability of both types of tumors. Louping-ill virus, which so far seemed to affect the viability of each type of tumor tested, failed to do so in the one experiment performed with Wagner osteogenic sarcoma. Although the rate of growth of the louping-ill-infected tumor fragments was slower than that of the controls, finally, in four of the five implanted mice, tumors grew to quite sizeable proportions. These results seem particularly interesting because of the fact that the Venezuelan and West Nile viruses had uniformly interfered with both the Wagner and the Ridgeway osteogenic sarcomas (Tables 3, 4). The Eastern equine-encephalitis virus, which did not interfere with the viability of Ridgeway osteogenic sarcoma, attained quite

high concentration in the tumor tissue, in contrast to observations with sarcoma 180 (Table 1).

A number of experiments were performed with the Patterson mouse lymphosarcoma. The results with the West Nile and Venezuelan viruses were irregular and erratic, but it should be pointed out that work with this tumor presents much greater difficulties. The rate of growth of the tumor is not uniform, and experiments were often conducted with mice bearing sizeable tumors before infection with viruses was induced. This may account for some of the puzzling failures observed with the Patterson lymphosarcoma, and additional experimentation is required before any conclusions can be drawn.

COMMENTS

In the analysis of the data presented here, one should bear in mind the factor of experimental error that is inherent in

TABLE 5

INTERFERING EFFECT OF CERTAIN NEUROTROPIC VIRUSES ON THE VIABILITY OF TRANSPLANTABLE MOUSE TUMORS OTHER THAN SARCOMA 180

Tumor type	Virus strain	Virus inoculated after tumor implant days	LD ₅₀ virus titer in tumor tissue	Results of bioassay; transplants originating from*		
				Virus-inoculated mice		Noninfected controls
				Ratio of tumor-bearing mice*	Size of tumors†	Ratio of tumor-bearing mice*
Methyl-cholanthrene induced sarcoma	Japanese B	6	10 ^{-1.00}	2:2	Same	4:4
	Japanese B	7	10 ^{-1.90}	5:5	Smaller	5:5
	Semliki	6	10 ^{-3.00}	3:3	Same	5:5
	Bunyamwera	6	10 ^{-1.70}	6:6	Same	6:6
	Bunyamwera	7	10 ^{-3.90}	5:5	Smaller	5:5
	Louping-ill	6	>10 ^{-6.00}	0:5	No growth	5:5
	St. Louis	6	>10 ^{-5.00}	0:5	No growth	5:5
	Ilhéus	7	10 ^{-1.50}	0:6	No growth	5:6
Adeno-carcinoma EO 771	Japanese B	12	10 ^{-2.00}	4:4	Same	5:5
	Semliki	6	>10 ^{-2.00}	5:5	Same	5:5
	Bunyamwera	6	>10 ^{-2.00}	3:3	Smaller	4:4
	Louping-ill	7	10 ^{-1.00}	0:5	No growth	5:5
	St. Louis	6	10 ^{-3.70}	1:4	Smaller	4:4
	Ilhéus	6	10 ^{-2.90}	0:5	No growth	5:5
	Ilhéus	12	>10 ^{-2.00}	5:5	Same	5:5
Wagner osteogenic sarcoma	Bunyamwera	14	10 ^{-1.00}	1:5	Smaller	6:6
	Louping-ill	14	10 ^{-2.00}	4:5	Smaller	6:6
	St. Louis	14	10 ^{-1.00}	4:5	Smaller	3:4
Ridgeway osteogenic sarcoma	Eastern equine encephalitis	14	10 ^{-2.00}	4:5	Same	4:5
	Russian spring-summer	14	10 ^{-2.90}	0:4	No growth	4:4
	Bunyamwera	14	10 ^{-3.20}	0:4	No growth	4:4

* Antecedent = number of mice with measurable tumors, consequent = number of mice implanted with tumor cubes.

† Compared on the same day after transplantation with tumors originating from noninfected control mice.

such types of investigations. Apart from the variability in growth rates and in regression rates among the different types of transplantable mouse tumors, introduction of a viral agent may lead to further variations. For the bioassays, only six 2-mm. cubes of tissue were employed from each tumor which, in case of interference, poses still another question: whether or not these particular fragments contained viable cells in sufficient numbers to start fresh tumor growth. The term "interference with viability of cells," therefore, must be taken with certain reservations in mind. According to Zahl and Drasher, there must be at least 20,000 viable cells in a fragment of sarcoma 180 to obtain successful transplantation. If the number of viable cells is reduced to 5000 or 1000, the number of takes will reach zero and no tumor will grow on bioassay. The number of viable cells may be markedly decreased as a result of virus infection, but the possibility is not excluded that there are viable neoplastic cells still present in virus-infected tumor tissue. Even when all of these factors are taken into consideration, one is probably justified only to comment upon the general trend in the results of the experiments, rather than to discuss the specific results of particular experiments.

The viruses that parasitized sarcoma 180 fall into two main categories—louping-ill, West Nile, Ilhéus, and St. Louis encephalitis, which caused total or partial interference with the viability of tumor cells; and Semliki Forest, Bunyamwera, and Japanese B encephalitis, which, in a rather limited number of experiments, showed no interference. With the exception of Eastern equine-encephalitis virus, all of the viruses inoculated into mice bearing sarcoma 180 were recovered from neoplastic tissues in titers equal to, or slightly lower than, in infected mouse brain. In the Eastern equine-encephalitis experiments, the pathogen was absent from the tumor tissue and no interference occurred with the viability of the tumor cells.

The Venezuelan equine-encephalomye-

litis virus stands out from among all of the other so-called neurotropic viruses, not only because of its high invasive power, virulence, and wide host range, but also because of its erratic behavior in tumors. Its oncolytic power was clearly demonstrated in many experiments in which the growth of the original tumors was arrested when infection with the Venezuelan virus took place. However, the results of bioassays in some instances indicated that an active interference with the viability of the tumor cells had occurred, but in others the transplants gave rise to tumors of size equal to that of the controls. This apparently erratic behavior becomes less paradoxical if viewed in the light of the work reported by Zahl and Drasher. If one postulates that the effect of Venezuelan virus is not uniformly spread throughout the tumor tissue and that some cells are affected while others remain still viable, the factor of chance must be given consideration; the particular fragments used for transplantation might or might not have contained enough viable cells to start new growth.

With the methylcholanthrene-induced sarcoma and adenocarcinoma EO 771, the general trend of results was similar to that observed with sarcoma 180 except that the factor of experimental error was much greater because of the limited number of experiments. However, West Nile, Ilhéus, St. Louis, and louping-ill viruses showed interfering effects with the viability of the two types of tumors, whereas, Japanese B (two experiments), Semliki Forest (one experiment), and Bunyamwera (two experiments) failed to do so. Erratic results were observed again when Venezuelan virus was used as the infecting agent.

When the Wagner and Ridgeway osteogenic sarcomas were used as test tumors, both West Nile and Venezuelan viruses interfered to a marked degree with their viability, since no positive results were obtained on bioassay. Of rather surprising nature was the observation that the Bunyamwera virus, which in all previous ex-

periments with other tumors failed to show any interfering ability, in the single experiments with Wagner and Ridgeway tumors showed definite oncolytic effect (Table 4). On the other hand, louping-ill and St. Louis encephalitis viruses had little or no interfering effect on the viability of the Wagner osteogenic-sarcoma cells. The Eastern equine-encephalitis virus, which failed to parasitize sarcoma 180, was present in Ridgeway osteogenic-sarcoma tissue (10^{-5} to 10^{-6}) but produced no interfering effect on the tumor growth.

These results seem to indicate that it is unwise to generalize on the behavior of viruses in relation to all transplantable mouse tumors, and that one should confine the analysis to the effect of a particular virus on one particular type of tumor without drawing any parallel conclusions. Furthermore, it should be pointed out that to bring about the interfering effect, a lethal virus infection of the mice was necessary.

The results of these investigations thus far have no practical aspect, nor do they constitute this year's cure for cancer. If anything, they underline the basic problems: What is the factor (or factors) that favors not only the multiplication of such immunologically unrelated viruses as West Nile and Ilhéus, or louping-ill and Venezuelan equine-encephalomyelitis, in tumor tissue but also leads to active interference with the oncotic process? Does, perhaps, a substrate exist in the tumor cells that is essential to the multiplication of certain viruses and that at the same time is necessary for the self-perpetuation of the oncotic

process? What is the relation of this hypothetical substrate to the one that may be present in the central nervous system? Answers to such questions must await further clarification of the metabolic processes involved both in tumor cells and in viruses.

SUMMARY

A study of the effect of infection with certain neurotropic viruses upon the viability of transplantable mouse tumors is reported.

The viruses of louping-ill, West Nile, Ilhéus, Russian spring-summer, and St. Louis encephalitis parasitized sarcoma 180 and showed either total or partial interference with the viability of the tumor cells. The viruses of Semliki Forest, Bunyamwera, and Japanese B encephalitis showed no interference with the viability of the tumor cells despite the presence of the viruses in tumor tissues. Eastern equine-encephalomyelitis virus was the only one of the group of viruses tested against sarcoma 180 that failed to parasitize the tumor tissue.

The viruses of French neurotropic yellow fever, Bwamba, Ntaya, Passos I, pseudorabies, and Western equine-encephalomyelitis failed to infect the mice by parenteral inoculations, and hence no effect on sarcoma 180 was observed.

Against the osteogenic sarcomas, the most consistent interfering effect was observed with the West Nile encephalitis and Venezuelan equine-encephalomyelitis viruses, and in one experiment, with the Bunyamwera virus.

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FURTHER STUDIES ON THE DESTRUCTIVE EFFECT OF THE VIRUS OF RUSSIAN FAR EAST ENCEPHA- LITIS ON THE TRANSPLANTABLE MOUSE SARCOMA 180

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THE destructive effect of the virus of Russian encephalitis on the transplantable mouse sarcoma 180 has already been reported.² In this communication are described some of the conditions under which the destruction takes place.

MATERIAL AND METHODS

Virus. A stock virus was prepared by removing brains aseptically from paralyzed mice and preserving them frozen in separate tubes at -40° C. When virus was needed, a brain was made into a 10 per cent suspension by grinding without abrasive with 10 per cent normal rabbit-serum-physiological saline. The appropriate dilution was then inoculated. The amount of virus in the supernatant was titrated by intracerebral inoculation in mice. It remained in the range of $10^{-5} \pm 1$ log.

Tumor. The transplantable mouse sarcoma 180 was used throughout the experiments. This rapidly growing, anaplastic tumor takes in 100 per cent of the transplants and attains a diameter of 10 to 15 mm. in one week.

Bioassay. The bioassay technique was relied upon to determine the extent of tumor destruction. Although histological examinations demonstrate necrosis, the ultimate criterion of destruction must be the ability of the tumor to grow. Following infection of the animal with Russian encephalitis virus, the tumor was removed and the least

necrotic pieces cut into 2-mm. cubes for implantation into mice immunized against the same virus. It was necessary to use immune mice because the tumor implants always carried enough of the infecting agent to cause the death of a nonimmunized animal in one to two weeks. Tumor measurements were made by calipers at weekly intervals after transplantation into the immune hosts. The percentage of growth was reported as the number of tumor pieces that grew in relation to the number implanted. Animals were observed for a period of four weeks. Whereas in many instances the transplants grew very slowly, they were classified as viable tumors.

Determinations of Virus Content. Whenever a tumor was transplanted to determine its viability (bioassay), one half was set aside for emulsification and determination of its virus content. At the same time, the brain of the tumor-bearing animal was removed aseptically and the amount of virus in it determined. The tissues were made up to 10 per cent in diluent and serial ten-fold dilutions made. Groups of three mice each were injected intracerebrally with 0.03 cc. of alternate dilutions. Although this method does not determine the titer as accurately as one might wish, it is adequate to allow the comparison of the amounts of virus present in different samples. The results obtained have been consistent. Titers have been calculated according to the Reed-Muench method for determining 50 per cent end points.³

Mice. Swiss mice obtained from commercial breeders were used for both tumor implantations and titrations. For the bioassay experiments, they were immunized by

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The work was done in part under a grant from the American Cancer Society.

Received for publication, March 22, 1950.

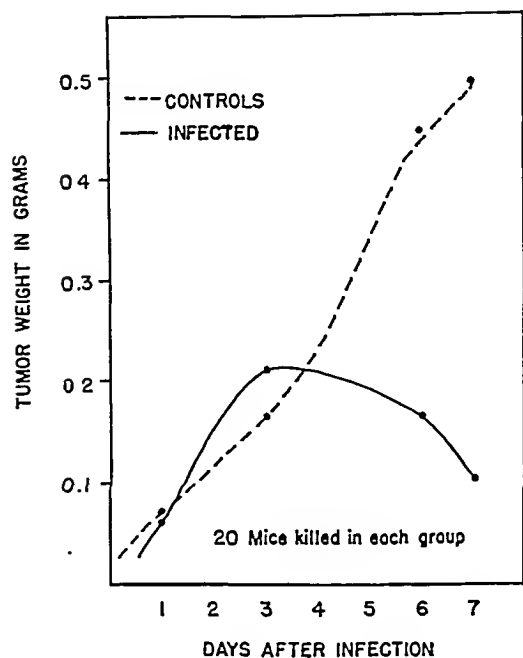


FIG. 1. Average weight of the sarcoma 180 after infection with the virus of Russian encephalitis.

the intraperitoneal injection of 0.2 cc. of a formalized mouse-brain vaccine prepared and administered according to the method of Casals and Olitsky.¹

RESULTS

Effect of Russian Encephalitis Infection on the Growth of the Sarcoma 180. It has been previously noted that following intraperitoneal inoculation of brain-suspension virus, the implanted tumors grew normally for two or three days, then their growth stopped.² In this experiment, groups of ten animals bearing tumors bilaterally implanted four days previously were inoculated intraperitoneally with 0.05 cc. of a 10^{-3} dilution of brain-suspension virus and killed at intervals thereafter. The average weights of the tumors from the infected and noninfected animals are shown in Fig. 1. The results confirm the observations previously reported. They indicate that no growth of the tumor takes place three days following infection of the host.

Effect of Different Amounts of Virus Inoculated Intraperitoneally on the Viability of the Sarcoma 180. These experiments were planned to determine the relation between the time necessary for complete destruction of the tumor and the amount of virus injected intraperitoneally. Mice bearing sarcoma 180 implanted four days previously were inoculated intraperitoneally with 0.05 cc. stock virus diluted to 10^{-1} , 10^{-2} , 10^{-3} , 10^{-4} , 10^{-5} . Tumors were removed at different days following inoculation, tested for viability by bioassay, and the amounts of virus determined in the tumors and brains of the sacrificed animals. The results are shown in Table 1 and graphically in Fig. 2.

It is apparent that the rapidity with which the tumor was destroyed depended upon the amount of virus inoculated. For example, when 0.05 cc. of a 10^{-1} dilution of virus was injected intraperitoneally (approximately 100,000 LD_{50} 's by the intraperitoneal route) no viable tumor cells are left three days after infection, but if the same amount of a 10^{-3} dilution (approximately 1000 LD_{50} 's) were inoculated, six days were necessary before the same effect was produced. The mice which received the 10^{-1} dilution died on the average of one day earlier than those receiving the 10^{-3} dilution although their tumors were destroyed three days earlier. As might be expected, the titrations of the brains showed that more virus was present when large amounts were injected. Little difference was observed in the tumors, however. More virus was found in the tumors than in the brains except when the animals were paralyzed or dying. In these instances, titrations of brains and tumors showed approximately equal amounts of virus.

Effect of Virus Inoculated Intraperitoneally on Tumors of Different Sizes. Mice bearing tumors one day, four days, and seven days after implantation were inoculated intraperitoneally with 0.05 cc. of a 10^{-3} dilution of virus. The tumors of mice implanted one day before inoculation failed

TABLE 1

EFFECT OF INOCULATION OF DIFFERENT DILUTIONS OF THE VIRUS OF RUSSIAN ENCEPHALITIS ON THE GROWTH OF SARCOMA 180

Dilution of virus inj.	Day of bioassay	Number of tumors bioassayed	% Of tumor destroyed	Amount of virus in brain*	Amount of virus in tumor*
10 ⁻¹	1	5	58	<1.0	5.5-6.0
	3	4	100	4.0-4.5	8.0-9.5
	4	3	100	4.0	7.5
	7	2	100	7.37	8.25
10 ⁻²	1	7	33	<1.0	4.0
	3	3	57	2.5	8.0
	4	3	78	<3.0	8.0
	7	3	100	8.5	8.5
10 ⁻³	1	2	0	<1.0	2.75-4.5
	3	2	40	2.75	8.5-8.75
	5	5	67	4.25-6.0	8.0-8.5
	6	7	100	8.25-8.75	6.75-8.5
	7	4	100	Not done	Not done
10 ⁻⁴	1	3	0	1.0	2.5
	3	3	0	2.75	6.75
	4	3	0	2.5	8.25
	5	3	70	>7.0	>9.0
	6	3	90	8.0	8.5
	7	3	93	6.75	8.5
	8	3	100	Not done	Not done
10 ⁻⁵	3	3	6	3.5	5.5
	5	10	43	4.0-4.5	8.0-8.5
	7	5	83	6.75	8.5
	8	4	100	8.0	8.0

* Expressed as the reciprocal of the LD₅₀.

to grow, hence no bioassay studies were possible. Only the totally necrotic implant was found when these mice were autopsied at death seven or eight days after inoculation. Bioassay of tumors that had grown for four days before inoculation showed that only partial destruction had taken place up to the sixth or seventh day after inoculation. After that time, no growth

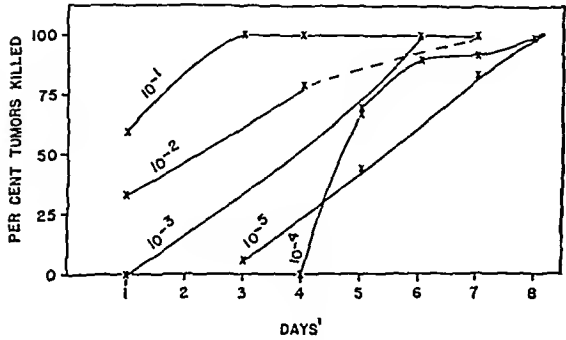


FIG. 2. Destruction of the sarcoma 180 in relation to the amount of Russian encephalitis virus injected intraperitoneally.

took place. Tumors that had grown seven days before inoculation showed the same susceptibility to the virus. Seven and eight days after infection, forty-five pieces cut from these tumors failed to grow when implanted into immune mice. There have been no indications that the age of the tumor or its size has any effect upon its susceptibility to destruction by the virus.

Effect on Tumor Viability of Virus Inoculated Intracerebrally or Subcutaneously. When 0.03 cc. of a 10⁻⁷ suspension of virus was inoculated intracerebrally into mice bearing five-day-old tumors, bioassay showed that the tumors were not viable six days later. One day after inoculation, when the titer in both the brain and tumor was less than 10⁻¹, the tumor pieces grew as well as the controls. Four days after inoculation when the titer in the brain was 10^{-6.0} and that in the tumor 10^{-3.75}, the viability of the tumor was still unimpaired. However, six days after inoculation when both tumor

and brain contained virus in equal amounts ($10^{8.5}$), the tumor failed to give a positive bioassay in immune mice. It appears, therefore, that even though the virus is inoculated into a most susceptible tissue, it finds its way to the tumor and is still capable of destroying it.

When virus was inoculated subcutaneously, tumor destruction took place to the same extent and at the same time as was the case following intraperitoneal inoculation.

Relative Susceptibility of Tumor Bearing and Non-Tumor-Bearing Animals to the Inoculation of Virus. It was noticed that animals bearing tumors appeared to die earlier following virus infection than did the control mice. Comparative virus titrations were therefore done on animals bearing four-day old tumors and on non tumor-bearing control mice. The 50 per cent end point for the tumor-bearing animals was $10^{9.0}$ and that of the controls was $10^{7.25}$. This result could be anticipated, since animals bearing tumors have much more susceptible tissue and are subjected to an overwhelming amount of virus.

Another study was made of the regression rate of tumors in animals that had been inoculated with noninfective amounts of virus intraperitoneally (e.g., 0.05 cc. of 10^9 to 10^{12}). The tumors of these animals showed no more regressions than did the uninoculated controls.

Attempts at Protecting the Animals Against the Virus Infection and Retaining the Tumor-Destroying Effect. The tumor-destroying effect of the virus infection has always been associated with the eventual paralysis and death of the animal. Many experiments have been done in an attempt to separate the tumor effect from the generalized one, but all have yielded negative results. Protection against the intracerebral infection has been attempted by the use of immune serums administered both intracerebrally and intraperitoneally, by partial immunization, and by inoculation of virus

directly into the tumor of immune mice. It has been possible to protect the mice against the infection by varying the time of administration of the virus and/or protecting agent. However, when the animal is protected, his tumor is unaffected, and when not protected, the tumor is destroyed. Attempts at controlling the virus infection by chemotherapeutic agents such as aureomycin, chloromycetin, and streptomycin have been unsuccessful.

DISCUSSION

More data have been presented to show the conditions under which the sarcoma 180 is destroyed during the course of infection with the virus of Russian encephalitis. The most important factor appears to be the presence of active infection. Although the tumor may be destroyed some days before the death of the animal, the virus eventually attacks the brain, producing paralysis and death. Attempts to separate the lethal and tumor destroying ability of the virus have so far been unsuccessful. The two factors may be inseparable but in at least one set of experiments,⁴ this virus has been shown to be effective in producing regressions in the tumors of RPL-12 fowl leukosis without fatal infection.

If it is possible to produce a strain or variant of the virus that might act in the desired way, it is necessary to have a base line against which such a strain could be judged. For that reason, the effect on tumor growth of various dilutions of a known stock virus was studied. It is also useful to know that the age of the tumor and route of inoculation make no difference in the ability of the virus to cause tumor destruction.

SUMMARY

Further proof has been presented that the virus of Russian Far East encephalitis is capable of destroying the transplantable mouse tumor, sarcoma 180. Destruction takes place irrespective of the age of the

tumor or the route of inoculation of the virus. The rapidity of destruction depends upon the amount of virus injected and has always been associated with the death of the animal although the tumor was de-

stroyed as long as three days before the fatal encephalitis. Attempts at preventing the encephalitis and maintaining the tumor-destroying ability have so far been unsuccessful.

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DEVELOPMENT OF MALIGNANT LYMPHOMA IN SOME OF THE YOUNG RATS SUCKLED BY MOTHERS RECEIVING METHYLCHOLANTHRENE BY STOMACH TUBE ONLY DURING THE LACTATION PERIOD

Preliminary Report

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WITH THE TECHNICAL ASSISTANCE OF
LILLY GLAZER

WE HAVE recently reported⁹ that the gastric instillation of methylcholanthrene is followed by the development, in very high incidence, of adenocarcinoma of the breast in female Wistar rats, with the appearance only rarely of a malignant tumor elsewhere in the body. These results raised certain questions: Did the breast cancers occur because of a preferential concentration of the absorbed carcinogen in breast tissue? Could the chemical carcinogen be excreted in the milk and, as a result, might malignancy be induced in the offspring suckled during a period when such carcinogens appear in the milk? The experiments reported herein were undertaken in an attempt to answer these questions.

MATERIAL, METHODS, AND RESULTS

All animals used in these experiments were grown in our own colony and derived from Wistar albino rats originally obtained from the Wistar Institute. At all times, inbreeding in our colony has been carefully avoided. Normal male and female

rats were mated. From eighteen to twenty-four hours after a litter was born, 2 mg. of methylcholanthrene in 0.5 cc. of olive oil was instilled into the mother's stomach through a catheter by a technique previously described.⁵ This instillation was repeated daily, six days of the week for a period of twenty-four days, a total of twenty-one instillations, until the offspring were weaned.

In view of the fact that Heidelberger and Jones have shown that the greater part of a carbon-labeled dibenzanthracene administered by stomach tube to mice will be expelled in the feces, great care was taken to prevent ingestion of any of the maternal feces by the offspring even though they were removed from the mother's cage before they were likely to seek food other than the mother's milk. The mother and offspring were housed in cages with bottoms of wide wire mesh that allowed the feces to drop from the cage immediately when voided, with only occasional exceptions. To guard against feces remaining in the cage, each cage was inspected frequently throughout the day and any fecal pellet that had failed to drop from the cage was removed.

At the end of the twenty-four-day period, each animal in the litter was placed in a separate cage and maintained on our fortified colony "Rockland" diet without further treatment.

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Aided in part by a grant from the National Cancer Institute, United States Public Health Service.

We are indebted to Dr. W. G. Dauben of the Radiation Laboratory, University of California, for supplying the carbon-labeled 20-methylcholanthrene.

Presented at 11st annual meeting of the American Association for Cancer Research, Atlantic City, April 16, 1950.

Received for publication, February 24, 1950.

Careful physical examination was made of each animal weekly, and complete blood counts were done after the third month of age at monthly intervals, except in Group 1 mentioned later, in which blood counts were not started until the animals were 12 months of age. Each animal was weighed twice a week.

Unfortunately, a defect in the air-conditioning system of our animal house recently resulted in the destruction of a large number of our experimental animals. However, we believe that our results available to date are sufficiently interesting and provocative to warrant a preliminary report at this time, since a repetition of the same experiments would involve at least eighteen months to reach the stage at which our other animals were destroyed. Such experiments, however, are now in progress.

The first group (Group 1) of offspring, whose mothers had received methylcholanthrene during the period of lactation only, consisted of twenty-two males and fifty females, a total of seventy-two animals. All of these animals were born between January 7, 1948, and February 14, 1948.

A second group (Group 2) of animals, whose mothers during the period of lactation were treated exactly as in Group 1, consisting of twenty-two females and twenty-one males, were born between February 25, 1949, and March 30, 1949.

Reticulum-cell sarcoma arising in mesenteric lymph nodes, which infiltrated the wall of the intestine as well as the stomach and pancreas, was found in two of the males in Group 1 at 10 and 13 months of age, respectively. No other neoplasms were detected in this group in animals between 16 and 17 months of age up to the date of the accident already noted (June 20, 1949). In Group 2, one male rat died with lymphatic leukemia at 86 days of age. Although no count on the peripheral blood had been taken at this early date, a blood smear taken from heart blood showed the following differential count: polymorphonuclears, 4 per cent; small lymphocytes, 20 per cent; lymphoblasts, 76 per cent; one nucleated red cell per 100 white cells.

The significant gross findings in this animal at autopsy were: the spleen was large, weighed 3.4 gm., and measured $5.3 \times 1.4 \times 0.4$ cm.; the liver was enlarged and weighed 8.4 gm.; the kidneys were large and hemorrhagic, and the mesenteric lymph nodes and those adjacent to the thymus were enlarged.

Histologically, the liver, lungs, cortical interstitial tissue of the kidneys, seminal vesicles, prostate, and muscularis of the stomach showed a marked infiltration by small, hyperchromic round cells, and in the spleen and lymph nodes, this infiltration completely replaced the normal architecture of these tissues. The heart muscle showed a nodular-like infiltration with leukemic cells. The pancreas was moderately infiltrated, while the testes appeared to have escaped infiltration.

These results suggested that the carcinogen might have been transferred to the offspring by way of the mother's milk. To obtain further information on this point, experiments were undertaken, using the tracer technique with carbon-labeled 20-methylcholanthrene.³ It was prepared synthetically with an over-all activity of 100,000 counts per minute per milligram carbon and with the activity in the 11-position. This substance, in the amount of 20 mg., was dissolved in 5 cc. of olive oil. When this solution was counted by us as an "infinitely thick" layer in a dish 5 sq. cm. in area, it had an activity of 1192 counts per minute. A lactating rat that had received daily 8 mg. of nontagged methylcholanthrene by stomach catheter for three days after she gave birth to her litter, was then given 0.5 cc. of olive-oil solution of the tagged methylcholanthrene by the same route daily for the next seven days. During the day on which the last dose of tagged methylcholanthrene was administered to the lactating mother, the five offspring, now 11 days of age, were anesthetized with ether. Each animal was skinned completely. The stomach was removed and through an incision along the greater curvature, the curdled milk was easily removed in its

TABLE 1

SPECIFIC ACTIVITIES OF UNSAPONIFIABLE MATTER EXTRACTED FROM SUCKLINGS

Fraction (sucklings)	Weight of extract (mg.)	Activity counts/min.
Carcass	328	1
Skin	220	1
Gastrointestinal tract	148	10
Liver	110	6
Milk (taken from stomachs of young)	27	34

entirety, as a coagulated mass. The skinned carcasses were divided into three additional fractions; (1) the emptied stomachs and the remainder of the intestinal tracts, (2) the livers, and (3) the rest of the bodies. The body of the lactating mother was separated into the following fractions: (1) tissue of breast areas separated from covering skin, (2) skin and remainder of subcutaneous fat, (3) gastrointestinal tract, (4) liver, and (5) blood. In addition, an extract was prepared from the feces collected during the entire period in which the animal had received the tagged carcinogen; and a sample of the urine was prepared by evaporation in a counting dish.

The tissues were ground and separately extracted with 95 per cent ethanol. The alcoholic extracts were then evaporated, and the lipid residues were dissolved in petroleum ether. The crude lipid fractions thus obtained were submitted to saponification by four hours reflux with 2 M alkali in 95 per cent ethanol and the unsaponifiable matter separated by extraction with petroleum ether. The activity of each of the fractions was then determined thus.

The extracts of unsaponifiable matter or aliquots thereof were placed in shallow metal dishes, 5 sq. cm. in area, and evaporated to dryness under an infrared lamp. They were then counted under an end-window counter. The activities as given are counts per minute per dish; since all samples were of "infinite thickness" and counted under similar conditions, the values given are approximations of the specific activities. Because of the low activities observed and the limited amounts of material available for analysis, attempts to obtain more precise figures for specific

activities or to calculate total activities seemed unwarranted.

The radioactivities of the fractions obtained from the bodies of the suckling rats are shown in Table 1. The activity of the milk, though low, is highly significant, since it is at least thirty times the probable error of the measurements. It is not certain, of course, that the activity of the milk represents unchanged methylcholanthrene. That this is probably so, however, was indicated in subsequent similar experiments in which nontagged methylcholanthrene was fed to lactating mothers. These experiments will be reported separately; in the extracts of milk recovered from the stomachs of the offspring, they show ultra-violet absorption peaks characteristic for methylcholanthrene.

The activity in the gastrointestinal tract of the suckling rats could be anticipated in view of the activity of the milk taken therefrom; but the activity of their livers is somewhat surprising, since no significant activity was found in the liver of the mother. Of the tissues of the mother (Table 2), only the gastrointestinal tract and feces displayed high activity; the activity of the skin and urine can be reasonably attributed to contamination by the radioactive feces. We have constantly been aware of the possibility of contamination of the young by the maternal excreta, but we feel that this can be ruled out in this experiment for the following reasons: (1) the skin of the sucklings had an extremely low activity, of the same order as the skinned carcass, despite the high activity of the mother's

TABLE 2

SPECIFIC ACTIVITIES OF UNSAPONIFIABLE MATTER EXTRACTED FROM VARIOUS TISSUES OF THE MOTHER

Fraction	Weight (mg.)	Activity counts/min.
Carcass	887	2
Skin	312	12
Gastrointestinal tract	246	94
Breast tissue	113	1
Liver	239	0
Urine		26
Blood	47	0
Feces	4829	253

feces; (2) the experiment was terminated when the sucklings were only 11 days old, at which time they would not eat solid food.

DISCUSSION

The occasional occurrence of lymphosarcoma in the rat has been recorded. Bullock and Curtis² report seventy-eight instances of sarcoma arising in the mesenteric lymph nodes among what they term 489 spontaneous tumors (found in 2450 rats) whose original source was apparently unknown. However, these tumors are not acceptable as spontaneous, since all but twenty-three of their animals had been fed eggs of *Taenia crassicolis*¹ whose larvae, they have reported, produce a high incidence of sarcoma of the liver. Ratcliffe, in 468 autopsies of rats of the Wistar albino colony, found two lymphoblastomas of the mediastinum, one lymphoid tumor of the thymus, and two lymphosarcomas. Farris and Yeakel, in autopsies in 1000 consecutive deaths of Wistar albino rats used for a study of the problem of aging, found nine reticulum-cell sarcomas, three in males and six in females that ranged in age from 331 to 555 days, a spontaneous incidence of this lesion of 0.9 per cent.

Of the seventy-two offspring in our Group 1, eleven died between the ages of 2 and 9 months from causes not related to any malignant process. Since the youngest animal in Farris and Yeakel's series to develop lymphosarcoma was approximately 11 months old, we felt justified in discarding from our calculations the eleven animals from this group that had died at earlier periods. Accordingly, the incidence of reticulum-cell lymphosarcoma in the remaining sixty-one animals of this group to the date of the accident already noted was 3.3 per cent.

Of particular interest, we believe, is the development of lymphatic leukemia in a 3-month-old animal in Group 2. Spontaneous lymphatic leukemia in the Wistar rat has thus far not been recorded. We are aware of only one case of spontaneous lymphatic

leukemia; this was reported in an inbred colony of Osborne-Mendel Stock by Wilens and Spioul. They also found eleven instances of myelogenous leukemia. The average age at death of the entire group of leukemias was 669 days for the females and 718 days for the males.

Since the essential unity of primary lymphatic tumors is now generally accepted, we may combine our findings in the two groups, making an incidence of three cases of malignant lymphoma in 104 offspring that might have ingested a carcinogen with the mother's milk while suckling, an incidence of 2.9 per cent. Comparing this incidence with that of nine in 1000 (0.9 per cent) for the Wistar control group, the difference between these two percentages considered to be normally distributed is unquestionably significant at the 1 per cent level (P is <0.01).

We believe that our results suggest a possible transfer of a chemical carcinogen, methylcholanthrene or some of its degradation products that are still carcinogenic, by way of the mother's milk to the offspring. Subsequently, in some of these, a malignant lymphoma was induced either in the form of a reticulum-cell sarcoma or lymphatic leukemia.

These results naturally invite some speculation relative to the problem of malignant lesions in man. Can they be significant in explaining the predominance of malignant lymphoma in children? Statistics compiled by the National Office of the American Cancer Society for 1946 show that, if accidental death is excluded, malignant disease is second as a cause of death in children from 1 to 14 years of age. Of these malignant processes, leukemia is the most common type.

The appearance of malignant lymphoma in our animals following the ingestion, while suckling, of a carcinogen that, chemically, is a steroid-related compound is not difficult to understand. From its chemical character, methylcholanthrene would most likely be absorbed from the intestine along with the fats and could lodge in greatest

concentration in the mesenteric lymph nodes toward which the intestinal lymph first drains. A possible mechanism that needs to be considered in cancer in children is whether the ingestion of carcinogenic substances, or the development of such substances in the mother during the lactation period because of some abnormal metabolic process, *might* result in the transfer to the suckling offspring of enough of the carcinogen to be responsible for the subsequent development of cancer in the child.

Fieser and Fieser have recently stressed the fact that methylcholanthrene, now recognized as probably the most potent known carcinogen, can be produced in the laboratory by chemical transformations of normal constituents (cholic acid and cholesterol) of the human organism; it is possible, they state, that the substance may arise in the body through a process of abnormal metabolism, especially since the reactions by which cholic acid is converted to the carcinogen in the laboratory are all known to occur normally in the animal body. While it is true that there is no evidence that methylcholanthrene or other hydrocarbon carcinogens play any role in the etiology of human cancer, there is also no evidence to exclude such a possibility. Fieser and Fieser speculate that a very minute amount of methylcholanthrene could produce a few malignant cells that, by cell division and without further stimulation

from the initiating agent, could lead to a palpable cancerous proliferation after an induction period, during which the initiating agent may have been eliminated from the system.

Results that we have obtained from the study of the distribution of the tagged carcinogen in the body of the lactating mother as well as from ultraviolet absorption studies of methylcholanthrene currently in progress, indicate that the quantity of methylcholanthrene that is absorbed, and that might conceivably supply the agent for initiating the malignant processes that we have seen in these and other experiments, must be minute indeed.

SUMMARY AND CONCLUSION

The gastric instillation of methylcholanthrene in the lactating Wistar rat was followed by the appearance of malignant lymphoma in some of the offspring. Following a similar instillation of carbon-labeled 20-methylcholanthrene in the lactating mother, we were able to extract from the milk, obtained from the stomachs of the sucklings sacrificed eleven days after birth, a material with a very significant activity count.

Both of these results, we believe, suggest that chemical carcinogens, either ingested or formed in the body of the lactating mother, may be transferred to the offspring by way of the milk, and, under suitable conditions, lead to malignant disease.

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THE EFFECT OF AZAGUANINE ON MITOSIS IN NORMAL AND NEOPLASTIC TISSUES

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THE carcinostatic activity of the guanine analog, azaguanine—5-amino-7-hydroxy-1*H*-*v*-triazolo[*d*]pyrimidine, on a variety of tumors in experimental animals has recently been reported⁵ and confirmed and extended in this laboratory.¹ In the present report, evidence will be presented that indicates that azaguanine has a specific effect on the mitotic activity of an undifferentiated squamous-cell carcinoma in rabbits (Brown-Pearce carcinoma). The observations of the actions of this chemical agent were made on tumors transplanted to the anterior chamber of rabbits' eyes and the potentialities of the Brown-Pearce carcinoma used in this way for studies in experimental cancer chemotherapy will be discussed.

MATERIAL AND METHODS

Fragments of the Brown-Pearce carcinoma were transplanted bilaterally to the anterior chambers of the eyes of rabbits of several breeds according to the method described by Greene. By careful attention to asepsis and to selection of viable tumor for transplantation, successful "takes" occurred in every instance. On the third day after insertion of the tumor fragment into the anterior chamber, vascularization by blood vessels from the iris had occurred and tumor viability was unmistakable by gross examination. At this time, the dimensions of the transplants were measured by

calipers and therapy was initiated. The daily intraperitoneal dosage of azaguanine ranged from 12.5 to 75 mg. per Kg. body weight. The control animals received comparable injections of the vehicle as previously described,¹ and the growth of each transplant was recorded by daily measurements. At the end of seven to ten days, the tumors in control animals completely filled the anterior chambers and the experiments were terminated. Procrastination beyond this time was followed by perforation of the cornea by the tumor with attendant hemorrhage. When this occurred, accurate estimation of tumor weights was impractical. After the animals were sacrificed, the eyeballs were removed and opened posteriorly; the iris with the intimately attached tumor was dissected out and weighed to the nearest milligram (Fig. 1).

Anterior-chamber transplants in more than two hundred rabbits have been made

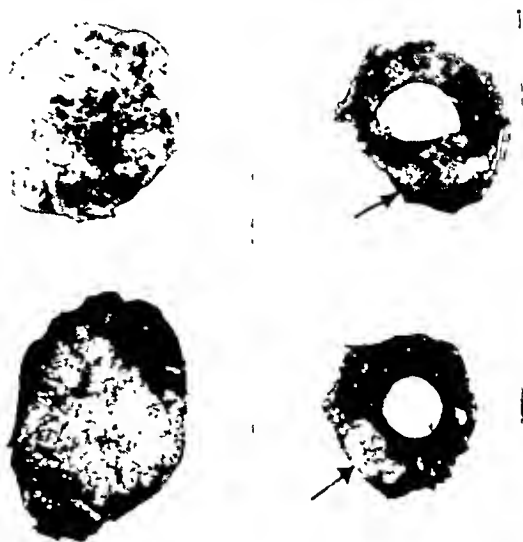


FIG. 1. Tumors after removal from eyes. Left, two tumors covering iris from untreated animal. Right, two tumors (arrows) with attached iris from treated animal.

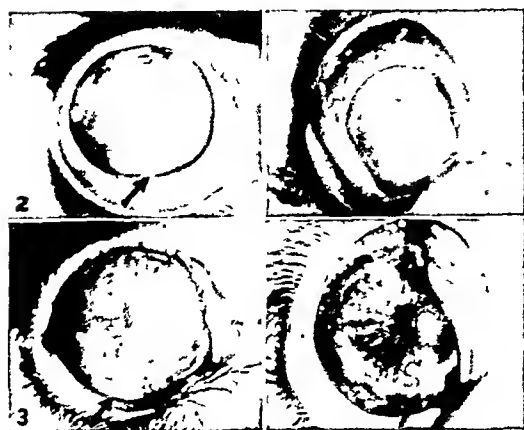
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This work was supported by a grant from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

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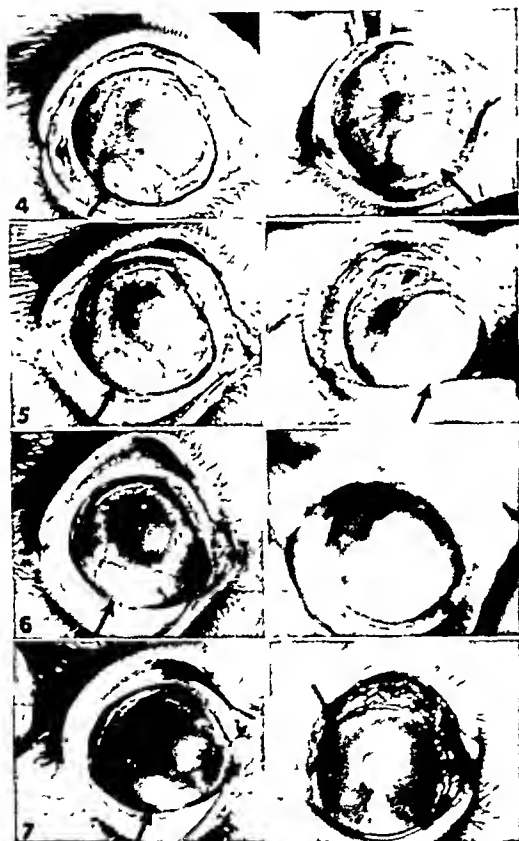
We wish to express our appreciation to Dr. H. S. N. Greene, Yale University School of Medicine, for generously supplying a tumor-bearing rabbit.

Received for publication, February 24, 1950.



Treated

Control



FIGS. 2-7. Sequential changes in anterior-chamber transplants of the Brown-Pearce carcinoma of an azaguanine-treated rabbit and an untreated control.

FIG. 2. Immediately after transplantation. Arrows point to tumor.

FIG. 3. Three days after transplantation. Therapy instituted at this time.

FIG. 4. Five days after transplantation.

and serial transplantation has not altered the growth rate or histological appearance of the tumors. It has been found that neither the sex of the host nor the breed has any apparent effect on the growth characteristics of the tumor. However, in any given experiment, animals of the same sex, age, and comparable weight have been used.

Histopathological studies have been made and described.¹

In the present experiments, the tumor-bearing animals were divided into four groups: untreated controls; azaguanine-treated; colchicized controls; colchicized azaguanine-treated. In the latter two groups, colchicine was administered intraperitoneally at a dose of 3 mg. per Kg. seven and a half hours before the animals were sacrificed. From all of the animals, tumor tissue, jejunum, and testis were prepared for histological study; the number of mitoses and the total number of cells were counted, with the aid of an ocular micrometer, in five separate high-power fields of each tissue.

RESULTS

Figures 2 to 7 illustrate the sequential changes observed in the tumor of an azaguanine-treated rabbit and an untreated control. Note that there is little change in the size of the tumor fragments of the treated animal after the initiation of therapy on the third day. This is a characteristic finding; regression of the tumor has not been observed. The results of azaguanine therapy on anterior-chamber transplants of the Brown-Pearce carcinoma are summarized in Table 1. A number of these experiments have been previously reported.¹

In Table 2, the complete protocol for the

FIG. 5. Seven days after transplantation.

FIG. 6. Eight days after transplantation.

FIG. 7. Ten days after transplantation. Experiment terminated since control tumor had filled the anterior chamber.

experiments on mitotic activity is recorded. There are several noteworthy features. As can be seen, the average number of mitoses in the tumor and in the jejunum of control and azaguanine-treated animals is less than in the colchicized counterparts. This demonstrates the action of colchicine in halting mitosis in metaphase so that mitotic figures are accumulated during the period of colchicine activity. These observations provide satisfactory evidence that an adequate dose of colchicine was administered to the animals and therefore a comparison of the proportion of mitoses between the colchicized control and colchicized azaguanine tissues is justifiable. It can also be seen that there is no significant difference between the mitotic counts in the testes of noncolchicized and colchicized animals. This finding confirms the surprising observations made by Guieysse-Pellissier who noted that colchicine failed to arrest mitoses in the testicular cells of rodents. The explanation for this fact is unknown.

Having established that the colchicine has had its anticipated effect, the pertinent results can now be confined to the observations on the colchicized animals. As can be seen, the incidence of mitosis in the tumors of untreated animals is consistently greater than that determined in the azagua-

nine-treated animals. On statistical evaluation, the probability that a difference in the mean percentage mitoses between the colchicized treated and colchicized control animals as large as that observed could occur by chance alone is approximately 3 in 1000. We therefore consider this difference to be significant. It will also be noted that the total number of cells per high-power field in the tumors of treated animals is appreciably less than noted for the controls. This is clearly shown in Figs. 8 to 11, which include photomicrographs of tumors from treated and control animals. It can be seen that the tumor cells of treated animals are considerably larger than those of control animals; the difference in the incidence of mitoses is also evident in these sections. A complete description of the morphological changes in the Brown-Pearce carcinoma induced by azaguanine has been published.¹

Returning to Table 2, it is to be noted that the mitotic rate in the jejunum and in the testis of colchicized, control, and azaguanine-treated, animals is essentially the same. It is the comparison between these findings and those noted in the tumors that leads to our conclusion. No morphological differences were detected in the sections of jejunum or testis that distinguished control and azaguanine-treated animals.

TABLE 1

EFFECT OF AZAGUANINE ON ANTERIOR-CHAMBER TRANSPLANTS OF BROWN-PEARCE CARCINOMA IN RABBITS

Exp. no	Group	No anterior-chamber tumor transplants	Initiation of therapy after transplantation (days)	Dose of azaguanine (mg/Kg)	Duration of therapy (days)	Mean tumor wt (mg)	Standard deviation (mg)	Standard deviation of mean (mg)	Average body weight (kg)	
									Beginning	End
1	Control	9			6	786	258	91	2.71	2.60
	Treated	8	3	75 O D	6	185	49	19	2.80	2.31
2	Control	8	3*			81	12	5		
	Control	10			6	515	75	25	2.59	2.56
	Treated	10	3	75 O D	6	96	9.7	3.2	2.55	2.17
3	Control	8			7	522	105	40	2.74	2.72
	Treated	6	3	12.5 O D	7	419	77	34	3.05	2.94
	Treated	6	3	25 O D	7	209	41	18	2.96	2.79
	Treated	6	3	50 O D.	7	156	22	10	2.77	2.27
4	Control	6			7	1058	360	161	3.07	2.73
	Treated	10	3	25 O D.	7	177	85	28	2.71	2.55

* Animals sacrificed to determine mean tumor weight at initiation of therapy.

TABLE 2

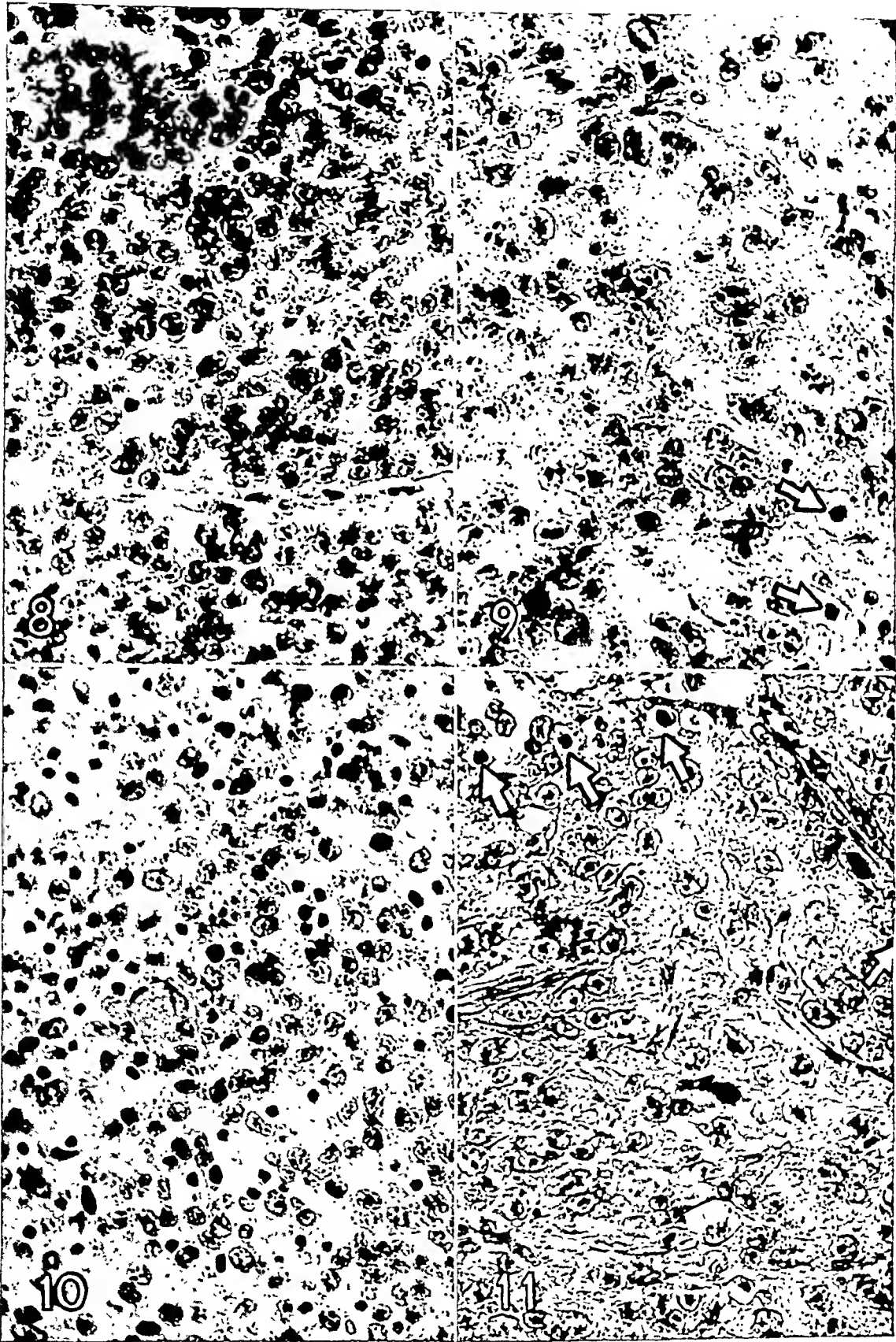
THE EFFECT OF AZAGUANINE ON THE MITOTIC RATE OF NORMAL AND NEOPLASTIC TISSUES IN RABBITS

	Tumor				Intestine				Testis			
	Cells/ hpf	Mit / hpf	Mit / hpf (%)	Mean mitoses (%)	Cells/ hpf	Mit / hpf	Mit / hpf (%)	Mean mitoses (%)	Cells/ hpf	Mit / hpf	Mit / hpf (%)	Mean mitoses (%)
Control	984 710 665 802 770	6 11 7 8 5	0.61 1.55 1.05 0.99 0.65	0.97	1075 1445 1332 1687 1618	6 11 7 11 15	0.56 0.76 0.53 0.65 0.92	0.68	551 604 330 382 383	84 164 37 43 21	15.24 27.15 11.21 11.24 6.11	14.19
TOTAL	1931	37	4.85		7157	50	3.42		2250	349	70.95	
Azaguanine	397 377 332 345 353	1 1 2 2 1	0.24 0.20 0.60 0.50 0.20		1326 1410 1056 1202 1196	13 12 11 11 13	0.98 0.85 1.03 0.91 1.08		568 406 506 622 580	102 40 68 63 110	17.95 9.85 13.44 10.12 18.96	
TOTAL	1804	7	1.74	0.35	6180	60	4.85	1.08	2682	383	70.32	13.84
	427 413 309 469 370	0 1 1 3 2	0.00 0.24 0.32 0.64 0.54		1296 1257 1192 1020 1272	16 10 21 14 11	1.23 0.79 1.77 1.37 0.86		380 391 354 372 403	56 52 45 54 52	14.75 13.30 12.70 14.50 12.79	
TOTAL	1988	7	1.74		6037	72	6.02		1900	259	68.04	
Colchicine control	703 729 745 830 758	59 61 70 104 84	8.40 8.37 9.40 12.53 11.08		1028 936 1081 943 1018	59 57 49 30 73	5.74 6.09 4.53 3.09 7.16		335 273 332 677 455	27 53 51 79 68	8.05 19.45 15.38 11.67 14.95	
TOTAL	3765	378	49.80	8.81	5006	268	26.61	6.25	2072	278	69.50	13.02
	620 806 917 825 854	56 63 72 65 49	9.03 7.82 7.85 7.88 5.74		1331 1241 1319 1076 922	72 103 94 81 70	5.40 8.31 7.13 7.53 7.60		506 470 277 309 270	86 39 28 41 40	16.95 8.30 10.12 10.50 14.80	
TOTAL	4022	305	38.32		5889	420	35.97		1832	234	60.67	
Azaguanine + colchicine	364 336 414 525 462	2 4 6 5 5	0.55 1.19 1.45 0.95 1.08		1194 1187 1109 1104 1169	52 79 76 92 96	4.36 6.66 6.86 8.32 8.24		287 195 310 233 292	35 21 64 21 28	12.20 10.79 20.62 9.03 9.60	
TOTAL	2101	22	5.22		5763	395	34.44		1317	169	62.24	
	518 364 528 487 518	7 5 6 6 7	1.35 1.37 1.14 1.23 1.35	1.31	872 869 784 782 654	54 48 58 39 42	6.19 5.53 7.41 4.93 6.43	6.26	296 405 462 398 411	61 38 68 68 63	20.60 9.38 14.70 17.08 15.33	14.11
TOTAL	2415	31	6.44		3961	241	30.49		1972	298	77.09	
	414 474 317 271 335	5 6 5 6 6	1.21 1.27 1.58 2.21 1.79		860 774 750 774 739	32 49 57 51 35	3.72 6.34 7.60 6.60 4.74		609 338 535 391 418	61 66 79 52 64	10.05 19.50 14.26 13.30 15.30	
TOTAL	1811	28	8.06		3897	224	29.00		2291	322	72.41	

DISCUSSION

Among the prime prerequisites of a tumor that is to be useful in experimental chemotherapy studies, easy and successful transplantation and uniform, rapid growth without spontaneous regression are particularly important. There are a variety of tumors that meet these criteria in rats and

mice. But tumors with these characteristics have not been available in larger animals. The unavailability of uniform tumors in large animals has necessitated separate investigations of the antineoplastic effect of chemical agents in tumor-bearing mice and rats followed by pharmacological studies in larger experimental animals when indi-



(For captions see opposite page.)

cated. The potentialities of investigating chemotherapeutic effect and pharmacodynamics simultaneously would appear to be great.

The Brown-Pearce carcinoma is an undifferentiated squamous-cell epithelioma that, in its morphological appearance and its characteristic of causing death of the host by distant metastases, resembles similar tumors in man. From this standpoint, therefore, it would seem to be an excellent test object for experimental chemotherapy. When transplanted subcutaneously, however, successful and progressive growth occurs irregularly; when the tumor is placed in the muscles or intracutaneously, "takes" are observed with far greater regularity, but spontaneous regression follows in about one third of the experiments. Haagensen and Prime, who studied carefully the course of the tumor transplanted into these sites, concluded that its behavior was so unpredictable that therapeutic experiments would be too difficult to control satisfactorily. By the simple expedient of transplanting the tumor fragments to the anterior chamber of the eye, it has been found, in our experience, that the growth characteristics of the tumor are remarkably uniform and therefore very valuable in studying the effect of chemical agents on neoplastic tissue. Other advantages of anterior-chamber transplants are that the viability of the fragment can be easily determined, changes in size can be observed directly, and alterations within the tumor during a course of therapy can be followed macroscopically and in greater detail by inspection with a dissecting microscope.⁶ Furthermore, an objective measurement of tumor weight is facilitated by the ease with which the tumor can be removed from the anterior chamber.

In the experiments with azaguanine reported in this paper and the previous studies, it can be definitely concluded that the chemical compound inhibits the growth of the Brown-Pearce carcinoma. The examination of the mitotic activity in the neoplastic and normal tissue was undertaken to determine whether the observed inhibition was due to a direct effect on the tumor and, if so, whether it was specific for the malignant cells. The use of colchicine, which arrests mitosis in metaphase, was merely to facilitate the observations. The recorded findings that demonstrate that the incidence of mitosis in the tumors of azaguanine-treated animals is significantly less than in the tumors of control animals indicate that the chemical compound decreases the rate at which tumor cells enter into mitosis. This fact, together with the finding that the incidence of mitoses in the jejunal crypts and in the testes is essentially the same in both treated and untreated animals, permits the conclusion that the azaguanine has apparently both a direct and a specific effect on the mitotic rate of neoplastic cells. The slight qualification of the foregoing statement is necessitated by the fact that studies of mitotic rate were not made on all normal tissues of the body, and therefore a completely dogmatic conclusion is not justifiable. The small intestine and testes were selected because of the normally high rate of cell reproduction in the tissues.

The evidence which indicates that the purine analog, 5-amino-7-hydroxy-1*H*-*v*-triazolo[*d*]pyrimidine has a selective inhibitory action on malignant cells places this chemical compound in a unique position among experimental cancer chemotherapeutic agents.

FIG. 8. *Brown-Pearce carcinoma from untreated animal.* FIG. 9. *Tumor from treated animal. Note increased cell size and clumping of chromatin produced by azaguanine. Only two mitotic figures present.* FIG. 10. *Tumor from colchicized untreated rabbit. Note numerous colchicine arrests.* FIG. 11. *Tumor from colchicized, azaguanine-treated animal. Only four colchicine arrests present. (H. & E. $\times 581$.)*

SUMMARY

Anterior-chamber transplants of the Brown-Pearce carcinoma have been used successfully in the study of an antineoplastic compound. The usefulness of anterior-chamber transplants in the field of experimental cancer chemotherapy is discussed.

By means of histological techniques, 5-amino-7-hydroxy-1*H*-*v*-triazolo[*d*]pyrimidine (azaguanine) was found to have a specific inhibitory effect upon the Brown-Pearce tumor associated with a decrease in the rate of entrance of the tumor cells into mitosis. The mitotic rate of the jejunal crypt cells and testicular cells was not affected by the drug.

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CO-OPERATIVE EFFECTS OF ENDOCRINOLOGICAL FACTORS AND PROCESSES OF AGEING IN PRODUCING ADENOMA-LIKE STRUCTURES IN RATS

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THE actual aim of the present experiments was the investigation of the effects of progesterone; desoxycorticosterone acetate; androgenic, oestrogenic, and thyroid hormones; and hormones of the anterior hypophysis on the processes of ageing. A part of these experiments are described from the gerontological aspect elsewhere.¹⁷

In this paper are given only those unexpectedly obtained results that have a relationship to the development of adenomatous formations in male and female rats.

The hormones were administered singly or in various combinations. Investigation of the simultaneous effects of different hormones is important because (1) in the organism, all hormones are secreted simultaneously in a certain balanced ratio; (2) therefore, unless there is definite evidence of a single deficiency, treatment with one hormone only might produce respective hyperhormonisation, and a dangerous upset of the balance of the hormones might occur; (3) some hormones become effective, or their unfavourable action is neutralised, only when certain other hormones are present.

Hyperplastic structures and adenomas in the liver, thyroid, parathyroids, adrenals, thymus, and pancreas have been found by various investigators both in man and some animals. The literature on the subject was reviewed by Ewing and by Willis. They

conclude that many simple hyperplastic processes might lead through benign adenomas into malignant neoplasms. On the other hand, cessation of growth with degenerative changes is also frequent.

In particular, in the rat's organs, adenomas or adenocarcinomas were recorded in the mammary gland, ovaries, uterus, testes, kidneys, liver, gastro-intestinal tract, thymus, adrenals, hypophysis, and thyroid.^{4, 7, 9, 11, 22, 25, 26, 27, 28} The incidence of adenomas was found to be most frequent in the mammary gland, e.g., Curtis et al. recorded them in about 0.9 per cent of all female rats that reached the minimum tumour age (14 months). Thymic adenomas were frequently found also, but in some strains only; Curtis et al. recorded this in the case of the Copenhagen strain of rats. In this strain, the benign thymic tumours occurred in about 65.6 per cent and malignant, in about 6.4 per cent. When, however, the percentage of incidence of the thymic tumours was calculated for all strains of rats, it was equal to about 0.63 per cent for benign, and 0.16 per cent for malignant tumours.

The occurrence of the tumours in other organs was considerably less frequent. For example, in the liver, Curtis et al. found cystadenomas in 0.03 per cent, hepatomas in 0.004 per cent, and adenocarcinomas in 0.03 per cent. Adenomas of the adrenals were recorded in eight rats only.^{4, 9, 22, 26} Thyroid adenomas were also rare.^{7, 11, 28}

Andrew found the following senile changes in the pancreas of both rats and man: proliferation of inter- and intra-lobular ducts, often with formation of apparently solid masses of cells, appearance

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The authors wish to acknowledge that the establishment and work of the Unit was made possible by a donation from Lord Nuffield, and that the hospitality to the Unit has been extended by Professor I. G. F. Liddell in the Department of Physiology of Oxford University

Received for publication, April 10, 1950

TABLE 1

EXPERIMENT 1. NUMBER OF META-HYPERPLASTIC STRUCTURES IN ORGANS OF RATS TREATED WITH ANTERIOR HYPOPHYSIS EXTRACT AND OTHER HORMONES

Dosage groups	No. of rats in group	Number of structures* in				
		Thy-roid	Adre-nals	Pan-creas	Thy-mus	Liver
1. Controls	8	0	0	0	0	0
2. Progesterone+thyroid hormone	7	0	0	1	2	1
3. A. H. extract, 3 mg.	7	0	0	1	0	1
4. A. H. extract+thyroid hormone	7	0	0	1	1	0
5. A. H. extract+thyr. horm. +progesterone	7	0	0	0	2	3
6. A. H. extract+doca†	7	1	0	1	0	0
7. A. H. extract+androsterone	8	0	1	1	0	0
8. A. H. extract+androsterone+doca	9	3	0	3	1	2
9. Androsterone+doca	7	2	0	0	2	0
10. A. H. extract, 6 mg.	6	0	0	0	0	2
11. A. H. extract+thyr. horm. +progesterone	7	0	0	1	2	0
TOTAL	80	6	1	9	10	9

* In Tables 1 to 3, meta-hyperplasias, adenoma-like structures, and true adenomas were counted together for each group and termed as meta-hyperplastic structures.

† Desoxycorticosterone acetate.

of cystlike local expansions of these ducts, and degenerative changes in the exocrine cells.

As to the endocrine factors producing adenomas, Wegelin and Hellwig found some relationship of the thyroid adenomas to goitre, since these tumours were found in goitrous rats.

The significance of oestrogenic hormones in the development of tumours of the female reproductive system appears to be well established. The literature on the subject has been thoroughly reviewed by Greene and Brewer. Burrows recorded a thyroid adenoma in one mouse after prolonged administration of oestradiol.

Heiman and Krehbiel¹⁰ increased the incidence of breast hyperplasias, and even obtained adenomas in a few rats, after combined administration of antuitrin (anterior hypophysis extract) and oestradiol.

Since our experiments do not relate to the implanted tumours, the review of the literature concerning the effects of endocrine factors on these tumours will not be given here.

In human pathology, important observations of Cushing and Davidoff must be em-

phasised as related to the results obtained in the present experiments. In their monograph on the changes observed in various organs of patients with hyperpituitarism, in particular acromegaly, Cushing and Davidoff described hyperplastic adenomas in the thyroid, parathyroids, adrenals, and pancreas. Referring to a few other similar cases in the literature, Cushing and Davidoff state that "one might almost speak of acromegaly, indeed, as a disease characterised by a pluriglandular tendency to adenomatous formations." Thus, hypersecretion of oestradiol, anterior hypophysis, or thyroid hormones is suggested by the above observations as one of the possible causative factors in producing adenomas.

Another obvious factor, suggested by the same observations, is connected with the actual processes of ageing, since most adenomas were observed in older rats. Thus, e.g., Ratcliffe stated that about 75 per cent of tumours developed in rats 451 to 900 days old. Curtis et al. found an average age of tumour bearers to be seventeen and nine-tenths months in male rats, and twenty-one and eight-tenths months in females. The other observers, already mentioned, found the tumours also in senescent or senile rats.

TABLE 2

EXPERIMENTS 2 AND 3 POOLED. NUMBER OF META-HYPERPLASTIC STRUCTURES IN FEMALE RATS TREATED WITH SEX AND THYROID HORMONES

Dosage groups	No. of rats	Number of structures in					
		Para- thy- roid	thy- roids	Adre- nals	Pan- creas	Thy- mus	Liver
1. Controls	17	1	0	0	1	6	3
2. Androsterone	6	1	0	0	1	0	2
3. Testosterone prop.	16	2	0	1	4	7	4
4. Thyroid hormone	12	0	0	0	3	8	5
5. Oestradiol B.B.	11	4	0	0	1	5	3
6. Oestradiol B.B.+ thyroid hormone	6	0	0	0	0	4	3
7. Oestradiol B.B.+ progesterone	15	1	0	0	0	0	4
8. Oestradiol B.B.+pro- gesterone+thyroid hormone	6	0	1	0	1	3	3
9. Oestradiol B.B.+pro- gesterone+thyroid hormone+andro- sterone	16	1	0	0	2	10	4
10. Oestradiol B.B.+pro- gesterone+thyroid hormone+testos- terone prop.	16	2	0	0	4	10	6
TOTAL	121	12	1	1	17	59	37

MATERIALS AND METHODS

Five experiments were performed on normal intact rats, the age of which varied in different experiments from seventeen to twenty-seven months. The total of 201 females and 189 males was used. The rats of our strain start to show some external signs of ageing from the age of about 16 months: they begin to lose the smoothness and lustre of the fur, to show a considerable degree of relative hypoplasia^{12, 14} in some of the organs, and they become less agile in their movements. In Tables 1, 2, and 3 are given the arrangement of the animals into groups, the number of rats, and total number of meta-hyperplasias (simultaneous metaplastic and hyperplastic changes), adenoma-like structures, and adenomas, counted together for each group.

Experiments 2 and 3 have been described¹⁷ chiefly from the gerontological point of view. With the permission of the Editors of the Journal of Gerontology they are referred to in this paper in order to summarise all the data, and obtain a correct interpretation of the results obtained in all our experiments on the subject.

The duration of the experiments and the doses of the hormones used in different experiments were as follows:

Experiment 1. The duration of the experiment was forty-two days, and it was performed on eighty female rats aged about

17 months. As the source of anterior hypophysis hormones, A.H. extract of this gland (powder form, Organon Laboratories) was used in doses of 3 and 6 mg., four times a week. Desiccated thyroid was given by mouth in the form of an emulsion, 65 mg. three times a week. Progesterone was injected as an oily solution, 2 mg. four times a week, and androsterone in crystals, 1.6 mg. three or four times a week. Desoxycorticosterone acetate was implanted subcutaneously in the form of pellets of 25 mg. (Organon Laboratories).

Experiment 2. The duration of the experiment was sixty days. Sixty-two female rats aged 27 months were used. Hormones were administered in the following weekly doses: 5 to 7.5 mg. androsterone, 2 to 4 mg. testosterone propionate, 10 mg. progesterone, all as crystals in 5 per cent gum acacia aqueous solution; 85 mg. desiccated thyroid, twice a week. Oestradiol benzoate-butyrate, 0.015 mg., was injected three times during the first ten days only.

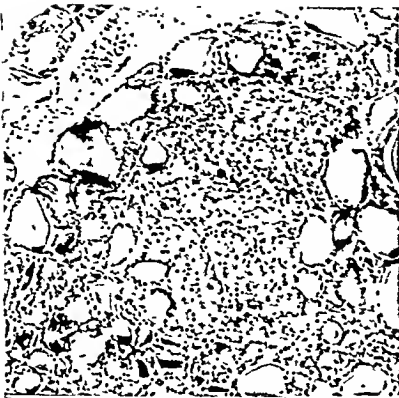
Experiment 3. The duration of the experiment was eighty-six days. It was performed on fifty-nine female rats, 22 to 24 months old. Doses of the hormones were given as follows: androsterone and progesterone, 10 mg. each, as crystals, once in ten days; testosterone propionate implanted subcutaneously as 20-mg. pellets; desiccated thyroid, 60 mg., three times a week; oestra-

TABLE 3
EXPERIMENTS 4 AND 5 POOLED. NUMBER OF META-HYPERPLASTIC STRUCTURES IN MALE RATS TREATED WITH SEX AND THYROID HORMONES AND DESOXYCORTICOSTERONE ACETATE

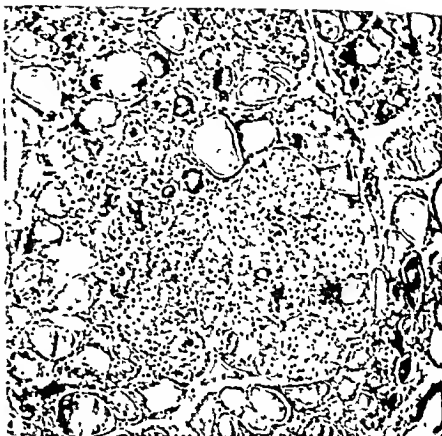
Dosage groups	Number of rats		Number of structures									
	Norm.	Cast.	Thyroid		Adrenals		Pancreas		Thymus		Liver	
Controls	13	13	3	2	1	0	0	1	4	4	7	4
Testost. prop.	12	12	2	1	3	4	0	5	3	4	7	4
Thyroid horm.	12	11	2	2	3	3	1	1	0	2	6	4
Oestradiol B. B.	9	7	2	2	3	3	3	0	4	2	3	3
Thyr. horm. + oestra- diol B. B.	6	6	0	3	3	2	0	1	1	4	2	5
Thyr. horm. + oestradiol + testost. prop.	13	11	3	2	2	0	2	2	5	3	7	3
Doca	6	7	0	2	2	1	0	0	0	2	2	4
Doca + thyroid hormone	7	6	0	0	1	0	1	0	1	2	4	3
Doca + testost. prop.	6	7	1	0	1	0	0	1	0	0	0	5
Doca + testost. prop. + thyroid hormone	7	5	0	3	0	0	0	1	1	0	4	4
Four hormones	6	7	2	3	0	0	0	3	2	0	3	4
TOTAL	97	92	15	20	19	13	7	15	21	23	45	43



1



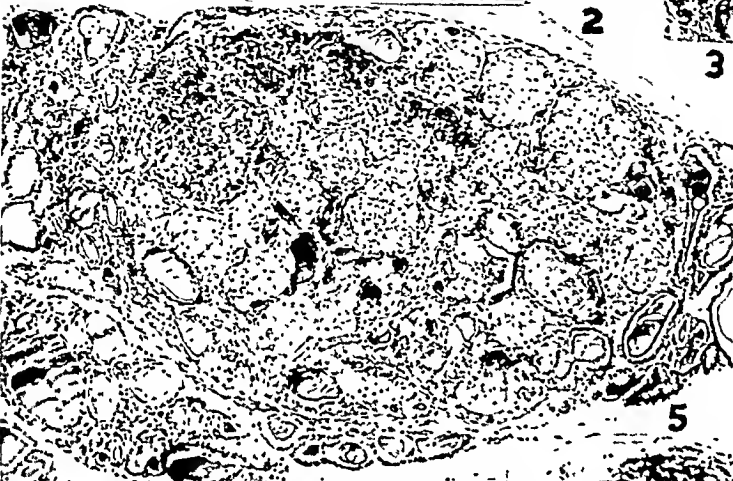
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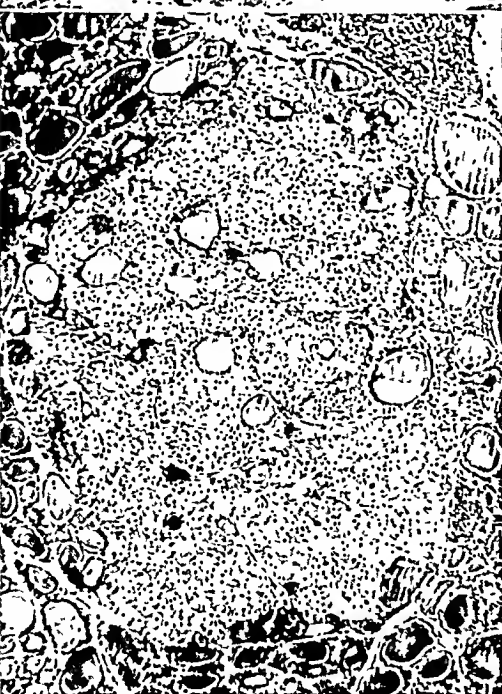
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(For captions see opposite page.)

diol benzoate-butyrate, 0.015 mg., twice during the first week only.

Experiment 4. The duration of the experiment was ninety-one days. One hundred twenty-three male rats, aged 21 months, were used, of which sixty-one were kept normal and intact, and sixty-two were castrated about one month before the beginning of the experiment. Testosterone propionate and desoxycorticosterone acetate were implanted subcutaneously as 25-mg. pellets. Desiccated thyroid was given by mouth, 24 to 43 mg. three times a week; 0.03 mg. of oestradiol benzoate-butyrate was injected subcutaneously twice, during the first week only.

Experiment 5. The duration of the experiment was sixty-eight days. Sixty-six male rats, aged about 20 months, were also divided into two series: thirty-six animals were kept normal and thirty were castrated about a month before the beginning of the experiment. Testosterone propionate was implanted subcutaneously in the form of 25-mg. pellets. Desiccated thyroid was given by mouth, 19.3 mg. three times a week; 0.016 mg. of oestradiol benzoate-butyrate was injected subcutaneously, three times during the first week only.

The results, obtained on females in experiments 2 and 3, have been pooled in Table 2; and those on males, in the experiments 4 and 5, have been pooled in Table 3.

The arrangement of the experiments is clear from the respective tables, namely the subdivision of the rats into groups injected with various hormones or their combinations, the number of rats in each group, and the number of the structures found.

The subdivision of the structures into various groups subject to the degree of their meta-hyperplastic changes was not made for two reasons: it is rather difficult to subdivide them in this way because of the transitional forms; from the point of view of their pathological significance a small meta-hyperplasia, with suitable conditions, might become an adenoma or carcinoma, as Ewing, Willis, and others rightly state.

Therefore, only in the text do we mention the number of those structures that we considered as adenomas. The accompanying photographs give a clear idea of the great variety of transitional forms obtained. In the present paper nearly all microphotographs were made of male rats, since those of the females were given in the other paper.¹⁷ All sections were stained with haematoxylin and eosin.

EXPERIMENTAL FINDINGS

Thyroid Gland. In the thyroid, the changes varied from minute nests of meta-hyperplasias to adenomas transforming nearly the whole of the gland (Figs. 1 to 7, 13).

FIGS. 1 to 3. Male control rats. In most intact rats, the structures of the thyroid were as small as in Fig. 1. The exceptionally large structures were found in three rats, one castrated control (Fig. 2) and two normal controls. Figure 3 represents one of these two controls. ($\times 63$.)

FIG. 4. Castrated male rat treated with thyroid hormone. The structure is similar to that of Fig. 1. ($\times 63$.)

FIG. 5. Normal male rat, treated with testosterone propionate. Large adenoma occupying about half of the thyroid. ($\times 63$.)

FIG. 6. Castrated male rat, treated with oestradiol benzoate-butyrate, and thyroid hormone. Compact adenoma of thyroid. ($\times 63$.)

FIG. 7. Normal male rat, treated with four hormones: testosterone propionate, desoxycorticosterone acetate, oestradiol benzoate-butyrate, and thyroid hormone. Spreading type of adenoma of thyroid. ($\times 63$.)

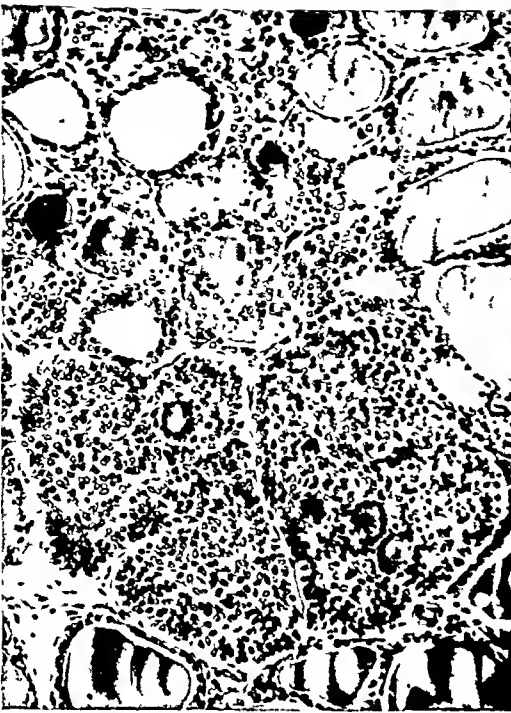


FIG. 8. Thyroid of control normal male rat. Form and size of the cells and nuclei in the structure are even. ($\times 140$.)

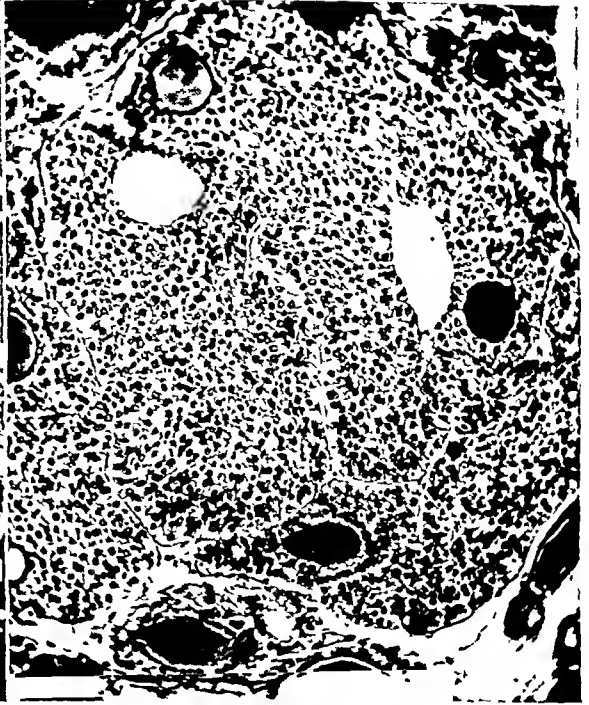


FIG. 9. Male normal rat treated with testosterone propionate and desoxycorticosterone acetate. Form and size of the cells and nuclei of the thyroid similar to those in Fig. 8. ($\times 140$.)



FIG. 10. Male normal rat treated with testosterone propionate, oestradiol benzoate-butyrate, and thyroid hormone. Thyroid structure consists of regular cylindrical cells (cylindroma). ($\times 140$.)



FIG. 11. Male normal rat treated with oestradiol benzoate-butyrate. A part of a large adenoma of the thyroid illustrated in Fig. 13 at $\times 28$. Disorganised growth of adenomatous cells, which, including their nuclei, vary in size and shape. ($\times 140$.)



FIG. 12. Normal male rat, treated with testosterone propionate, oestradiol benzoate-butyrate, and thyroid hormone. Disorganised growth of cells of thyroid, both the cells and nuclei varying in shape and size. In some acini, the cells secrete a fluid in which the single and grouped cells are floating. ($\times 140$.)

In the control intact animals, however, the largest structures never reached the size of those present in some of the treated animals. The two largest adenoma-like structures so far observed in our intact control animals are represented in Figs. 2 and 3. Moreover, in no control rat were the growth and variation in size and form of cells and nuclei observed to be as great histologically as in some of the treated animals. The comparison of Fig. 8 with Figs. 9 to 14 illustrates this well. In the detailed histology of both the "control" and "treated" structures, two features were common: namely, a tendency of the cells, sometimes in places only, to form a syncytium; and the larger size and vesicular character of the nuclei as compared with those of the normal thyroid epithelium.

In some of the treated animals, in addi-

tion, the variation in size and form of the epithelial cells and their nuclei was very great indeed (Figs. 11, 12, 14). Some of these cells acquired the spindle-like form of the sarcoma cells. A similar metaplasia of adenomatous or carcinomatous cells into sarcoma-like cells in the thyroid of mice was described by Slye et al. Loeb found thyroid tumour in a rat that had a sarcoma-like structure but that, during some transplantations, acquired the structure of endothelioma. While in some of the adenoma-like structures the cells kept the acinar structure, in others they broke this arrangement and spread irregularly in all directions. Very often, in the same adenoma-like structure or adenoma, these two cellular arrangements were very closely interwoven throughout the whole formation (Figs. 11, 12, 14).

Note must be made of a peculiar structure observed in one animal, simultaneously treated with testosterone propionate, thyroid hormone, and oestradiol. It consisted of acini or alveoli of high, cylindrical, narrow cells, predominantly of a regular

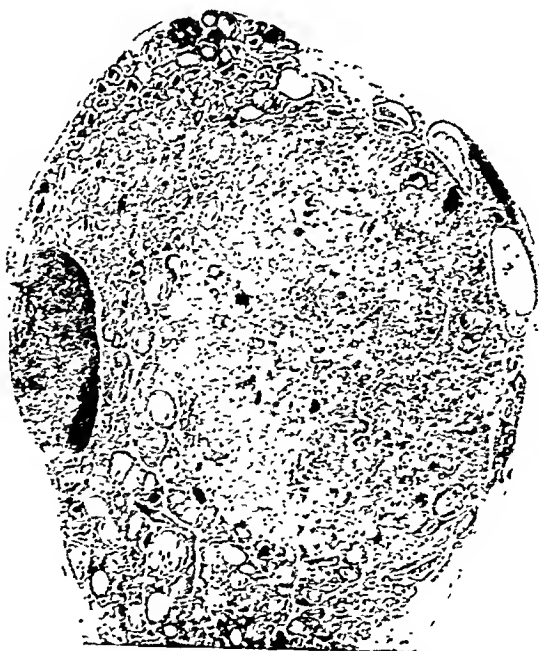


FIG. 13. Normal male rat, treated with oestradiol benzoate-butyrate. ($\times 28$.) Large adenoma, represented at medium magnification in Fig. 11.

shape, with vesicular nuclei situated towards the luminal part of the cytoplasm (Fig. 10).

It is necessary, however, to emphasise that in some of the treated animals, the structure was as small as that found in the controls (e.g., Fig. 4), and more or less as regular (Fig. 9) as that occurring in the untreated animals.

It is impossible to connect the histological peculiarities of the structures with the treatment of some special hormone or special combination of the hormones used. For example, as illustrated in the microphotographs, the largest and most disorganised were observed in both males and females after treatment with a single hormone only (testosterone propionate, oestradiol), or with various combinations of four or three hormones.

Parathyroids. A typical adenoma of the parathyroid was observed in one female rat only, treated simultaneously with progesterone, oestradiol benzoate-butyrate, and thyroid hormone. It has been described and illustrated in our other paper.¹⁷

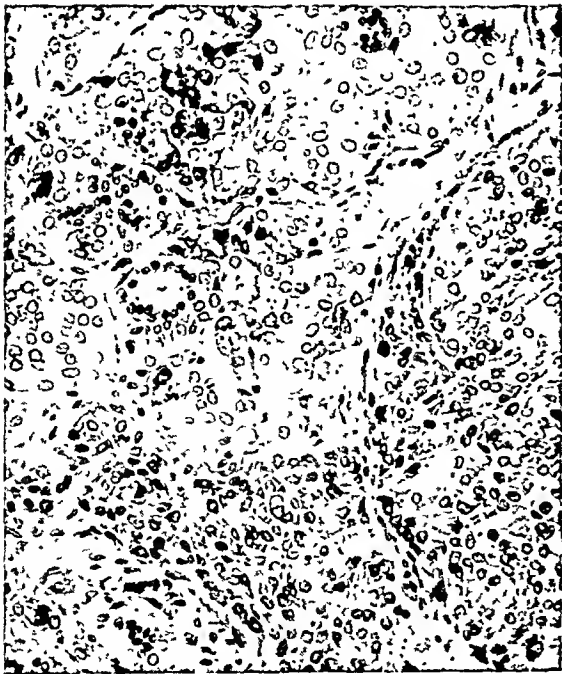


FIG. 14. The same rat as in Fig. 13, but at $\times 196$ to show the varying structure of cells, nuclei, and cytoplasm, differently stained in different cells. Some sarcoma-like cells.

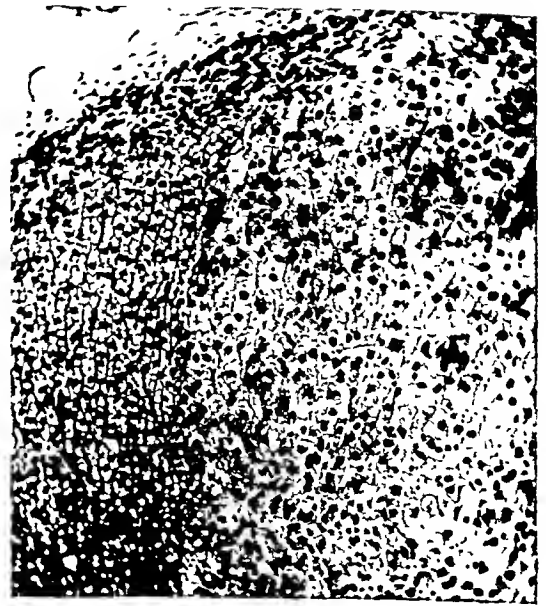


FIG. 15. Normal female rat treated with testosterone propionate. On the left side, can be seen the normal adrenal structure of the zona glomerulosa and zona fasciculata, transformed (on the right) into large metaplastic cells with enlarged nuclei of varying size, and much more dense cytoplasm. ($\times 140$.)

Adrenals. In the adrenals, two types of structures were found, namely, nodular meta-hyperplasias of the fasciculata cells; and extra-capsular structures, that apparently originated from the glomerulosa cells but that were later invaded by metaplastic fasciculata cells as well.

The first type is represented in Fig. 15. It consisted of much hypertrophied fasciculata cells with enlarged nuclei. In most cells, the cytoplasm was dense, containing very thin vacuoles or none, while in places the other cells contained vacuoles of varying size, mostly larger than those of the neighbouring fasciculata cells.

The structural cells were abruptly transformed from the normal fasciculata cells, so that the structure, although not possessing a capsule, was always sharply demarcated from the normal cortical cells. These structures were of varying sizes. The microphotograph of the largest structure at low magnification has been given elsewhere.¹⁷

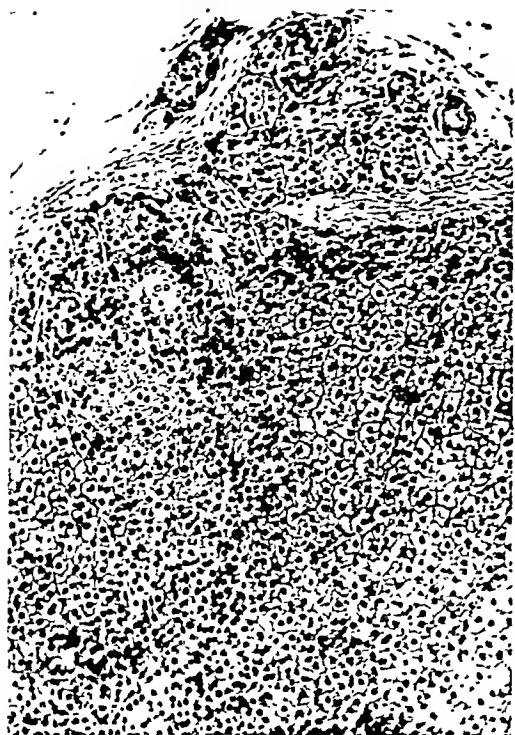


FIG. 16. Castrated male rat, treated with oestradiol benzoate-butyrate. Beginning of the formation of an extracapsular adenoma from glomerulosa cells, breaking through the capsule of the adrenal. On the left side of this first structure is superimposed a smaller second structure, formed by the breaking of the capsule of the first structure. Below the glomerulosa structure is a large dark nest of the fasciculata cells, starting their metaplasia. On the right, below the capsule, are normal glomerulosa and fasciculata zones. ($\times 140$.)

At a higher magnification, a part of it is represented in Fig. 15.

Similar single or multiple nodular hyperplasias or adenoma-like structures were also often found in, and connected with, ageing in man.^{6, 23} Ewing concludes that all gradations exist between simple local hyperplasias of the adrenocortical cells and their transformation into adenocarcinomas.

The second type of the cortical structure is represented in Figs. 16 to 22. This type consisted of nodules of hypertrophied glomerulosa cells, breaking through the adrenal capsule. Figure 16 illustrates such a start,

with a secondary structure breaking through the capsule of the primary structure. In all cases so far, a nodule of hypertrophied or metaplastic, or both, fasciculata cells (Figs. 16 to 20, 22) was seen below this hypertrophied nodule of glomerulosa cells. At the later stages, the structures developed into larger formations (Figs. 17, 19), in one case covering about half the adrenal, and could be defined as an adenoma (Fig. 21). At these stages ingrowth into, and presence of, metaplastic fasciculata cells in the structure are often found (Figs. 17 to 20, 22). Glomerulosa cells were also metaplastic, showing various forms and sizes both of cells and their nuclei (Figs. 20, 22).

Besides these two types of cells, a third kind was present in one case (Figs. 19, 20). These had water-clear cytoplasm, often

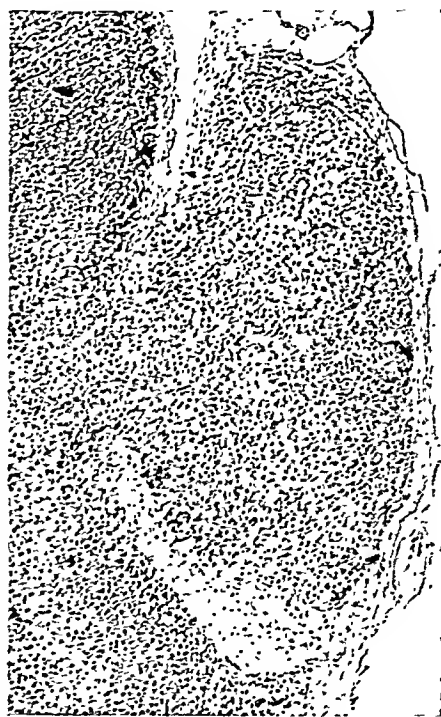


FIG. 17. The same rat as in Fig. 16. On the opposite side of the same adrenal a small, but fully developed, adenoma is formed. It consists of a mixture of glomerulosa (lightly stained) and fasciculata (darkly stained) cells. Broken capsule is in the middle of the photograph. ($\times 83$.)

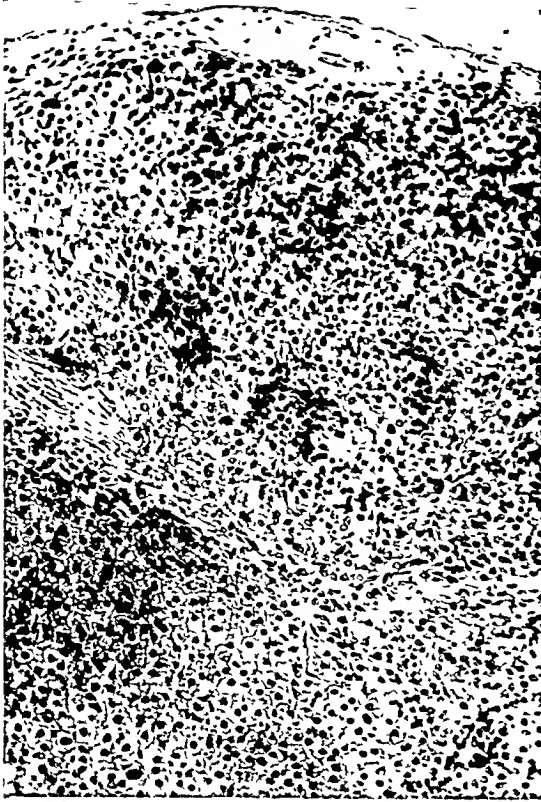


FIG. 18. The same rat as in Figs. 16 and 17. Part of a structure given in Fig. 17, showing disorganised growth of metaplastic glomerulosa and fasciculata cells. ($\times 140$.)

with shrunken or pyknotic nuclei. Their gradual transition from the metaplastic glomerulosa cells of the structure could easily be traced. Unfortunately, no part of the structure was available for fat stain. They produce an impression of degenerating, perhaps oedematous cells.

It is necessary to emphasise that not only outgrowth of the cortical elements and their development into the structure could be discovered, but also ingrowth of the structural cells into the cortical parenchyma (Figs. 18, 22) through the disrupted adrenal capsule, dividing the adrenal from the structure.

In addition to the proliferating processes in the structures, a haemorrhage into one of the fasciculata nodules was recorded with subsequent degeneration of the cells and formation of a haemorrhagic cyst (see Fig. 37).

Only one very small meta-hyperplastic

nodule was observed among the control animals. The remaining, most of them considerably larger, were present in the treated animals. With a comparatively small number of animals in each group and a small number of the structures found, it is impossible to connect them with any special hormone combination.

Pancreas. Examination of the pancreatic structures suggested three types: one, originating from the exocrine acinar cells; a second, from the smallest pancreatic ducts (confirming Andrew's results); and a third, from the islands of Langerhans. The structures were found in two of the control intact rats, one of which is represented in Fig. 27. They were not only more rare than in the treated animals but were also smaller than in some of the corresponding treated rats. They both belonged to the first type and contained several acini in a transitional stage.

The first type of structures developed from exocrine acini by loss of distinction in the basophilic and eosinophilic parts of the cytoplasm, narrowing of the cells resulting in the formation of a more or less large lumen, decrease in size and often flattening of the nuclei, which became lighter and poorer in chromatin. There were several transitional forms (Fig. 23). Mitoses were sometimes found in these metaplastic, newly formed follicles. In places, the cells became loose and formed cellular nests, giving a picture of solid adenomatous tissue.

In Figs. 24 to 26 is represented the formation of the second type of the pancreatic adenoma-like structures, namely, those chiefly from the smallest pancreatic ducts. Possibly, besides the ordinary ducts, there are also involved in the process those that were described by Maximow and Bloom as consisting of undifferentiated cells and taking part in the regeneration of pancreatic tissue. The latter ducts are in touch with the normal ducts and the islands of Langerhans. In these structures, the transitional forms from the acinar cells were not usually

found, or, if present, in a small number only.

In these structures, the proliferation of loose cells and formation of small solid nests from the proliferating ducts were also observed (Figs. 24, 25).

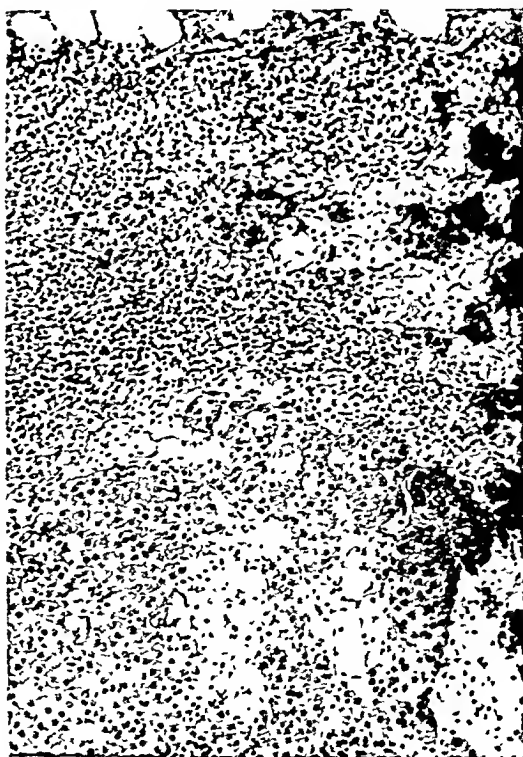
In a few cases, the formation of cystic dilatations of the structural ducts was seen. This spontaneous transformation was well described by Andrew in intact senile rats, from 800 to 1170 days old, i.e., older animals than those used in the present experiments. Figure 26 illustrates this cystic transformation.

The third type of meta-hyperplasia, namely from the islands of Langerhans, was observed in one rat only. It is illustrated in Figs. 30 and 32. When compared with the cells of gigantic islands (Fig. 31),

normally but exceptionally occurring in the pancreases of normal rats, the cells were much larger and had a different, densely granulated cytoplasm with large nuclei. At first glance, the cells of this structure have some resemblance to those of the corpus luteum or to some of the adrenal fasciculata cells.

Thymus. Previously,^{20, 21, 24} the small nests of meta-hyperplasias of epithelial thymic cells in adult rats were recorded; their development into considerably more frequent and larger structures, with the formation of small cysts, produced by oestradiol injections, was described; and literature on the subject given.

In the present experiments, the same meta-hyperplasias were found in senescent



FIGS. 19 and 20. *Castrated male rat treated with testosterone propionate. A small extracapsular adenoma of the adrenal (Fig. 19, $\times 83$, and Fig. 20, $\times 140$), consisting of three types of cells: metaplastic glomerulosa cells (small grey), large "water-clear" cells derived from the former, and metaplastic fasciculata cells (dark, large). Gradual transition of metaplastic glomerulosa cells into "water-clear" cells is clearly seen in the upper part of Fig. 20. "Water-clear" cells invade the fasciculata zone.*

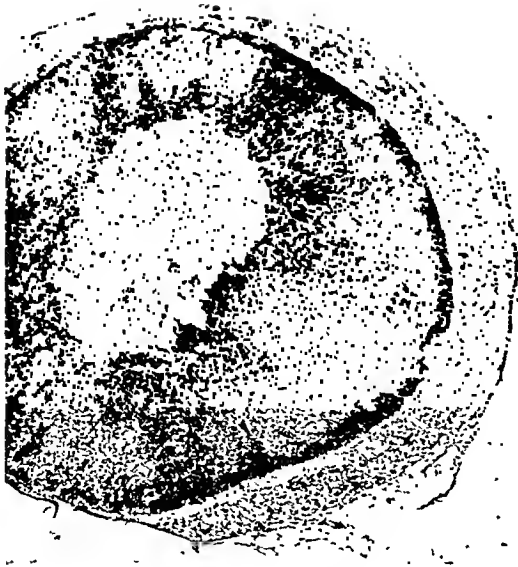


FIG. 21. *Castrated male rat treated with thyroid hormone. On the right side of the adrenal, large semicircular extracapsular adenoma formed from metaplastic glomerulosa cells. ($\times 21$.)*

intact rats. They were in the form of isolated small nests or ribbons. Their incidence in older male and female rats (Tables 2 and 3) was frequent (about 35 and 33 per cent respectively).

As before, much larger, adenoma-like structures were observed after treatment with oestradiol alone, or simultaneously with other hormones. These spread in the form of ribbons and nests—in three cases through the greatest part of the thymus, in places nearly, or completely, replacing the thymic parenchyma (Figs. 33, 34). In another case a solid tumour, which apparently could be defined as adenoma (thymoma), was observed (Figs. 35, 36). In all animals, the epithelial structural cells were of the same type, being mostly oblong in shape with vaguely demarcated cytoplasm and vesicular, usually also oblong, nuclei (Figs. 34, 36). In places, small cysts were scattered in the structural tissue.

As a peculiar feature in the development of these adenoma-like thymic structures in senescent rats, it is necessary to mention that in our breed of rats, their occurrence was considerably more frequent as com-

pared with young or adult animals; and they were present in the groups of rats treated not only with oestrogens, but also with testosterone propionate, or thyroid hormone, or desoxycorticosterone acetate. In addition, the formation of a solid thymoma was observed for the first time in our senescent rats.

In rats injected with androgens, alone or in combination with other hormones, the thymus was very atrophic, reduced chiefly to fat and fibrous tissues with a few small scattered nests of thymic parenchyma. The latter, however, consisted chiefly of epithelial cells, with a comparatively small number of thymocytes. In spite of being compressed by developing fibrous tissue, some of these small epithelial structures showed an adenoma-like shape and arrangement of the cells in some places.

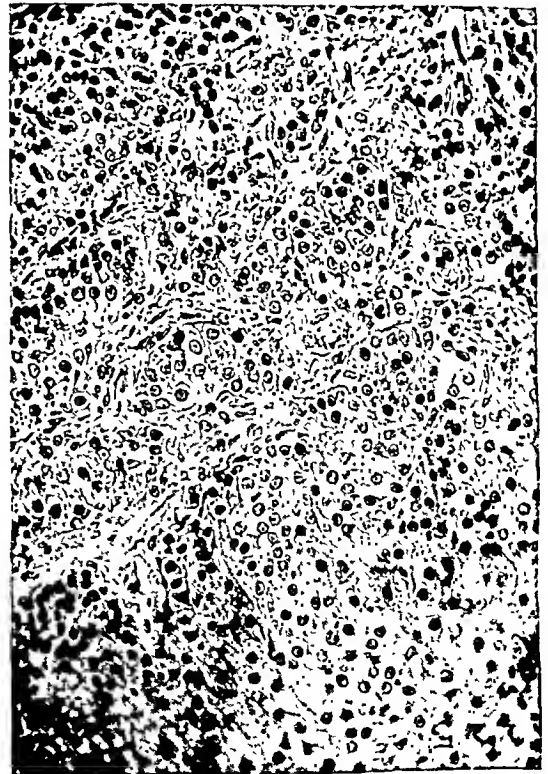


FIG. 22. *A part of the adenoma of the adrenal represented in Fig. 21 ($\times 225$). Disorganised growth of the adenomatous cells breaking through the adrenal capsule (remnants of the capsule on the lower left) into metaplastic zona fasciculata (darkly stained cells).*

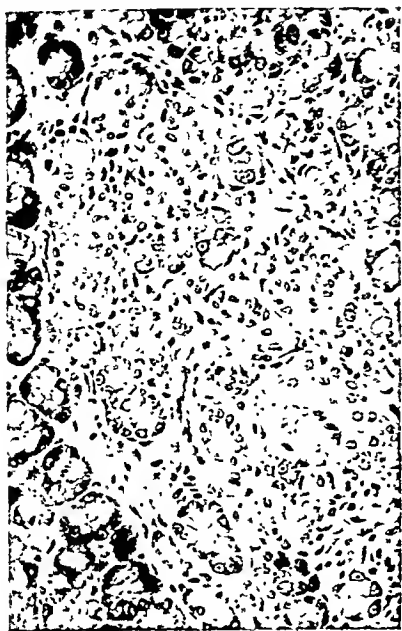


FIG. 23. *Castrated male rat, treated with testosterone propionate. Formation, in the pancreas, of adenoma-like structure (light cells) from the acini of exocrine cells (cells with granular cytoplasm, darkly stained at periphery). In the lower right, a small island of Langerhans compressed by neoplastic tissue. ($\times 225$.)*

Liver. Ewing divides liver tumours into three categories in connection with their origin (1) from liver cells, (2) from bile ducts, or (3) from both. As to the early stages in their development, he emphasises (p. 735) that "many of the simple hyperplastic processes lead through benign tumors into malignant neoplasms . . ." The hyperplastic structures obtained in the present experiments resemble the very beginning of development of multiple adenomas of bile ducts in man. Ewing describes them as follows (p. 750):

"The tumors lie beneath the capsule or deeper in the parenchyma [of the liver], and appear as grayish-white nodules 0.5 to 2 or 3 cm. in diameter. . . . The nodules are usually incased in connective tissue, and are free from bile deposits. The structure presents many small alveoli with definite lumina, lined by one or more layers of small cubical or higher cylindrical cells,

in which the nuclei are very prominent and the cytoplasm clear. . . . The lumina of the alveoli are usually empty or contain granular or hyaline detritus, but dilatation and lateral outgrowths may occur, polypoid projections may develop, and there are many transitions to cystadenoma and adenocarcinoma." Slye et al. described a similar tumour in the liver of an old rat. They defined it as adenocarcinoma.

In our rats, the bile-duct hyperplasias consisted of alveoli lined with the cubical or flattened epithelium, with clear cytoplasm, and round or flattened vesicular nuclei. The number of alveoli in the structures varied greatly, from a few to many, in different animals. Similarly, the number of structures in the liver also varied greatly, from one or two, to several, on a transverse section of a small hepatic lobule.

In Figs. 38 and 39 are represented the largest hyperplastic structures observed in the control animals of the present experiments. In experiments 1, 2, and 3, the difference between the control and treated female rats was in the absence of the liver structures (Table 1), or their smaller number (Table 2) in the control groups. Moreover, in these experiments, the largest structures were observed in the treated groups only. One of the most affected livers was found in a female rat treated with oestradiol benzoate-butyrate and belonging to experiment 2. It has been described elsewhere.¹⁷ However, in experiments 4 and 5 (Table 3) on males, the percentage of structures in the control rats was about the same as that in the treated animals. The difference in the size of structures was also not so definitely marked as in the female rats.

DISCUSSION

The number of rats in each group of the present experiments is too small to draw definite conclusions as to which of the hormones or their combinations has a strong or weak adenoma-producing effect, or no effect at all. For the same reason, it is impossible to say whether castration (Table 3) had any effect in this respect.

There are, however, some features that might be suggested as specific when considering the data in the Tables 1 to 3 and the results of histological examination. Thus, in experiment 1 (Table 1) on rats aged 17 months, i.e., the youngest animals used, as compared with those in experiments 2 to 5, there were not only no adenoma-like structures in the control groups, but not even simple meta-hyperplasias. From these data, it is possible to suggest that, on the whole, the spontaneous development of meta-hyperplasias in the intact, normal or castrated, rats of our breed occurred from the age of about 20 months on. In control rats of experiments 2 and 3 on senescent females, most of the organs investigated (except the adrenals and pancreas) had meta-hyperplasias, but nearly all of these were very small. An exception was a meta-hyperplasia found in the pancreas of one of the seventeen control rats. It affected the whole small lobule of the pan-

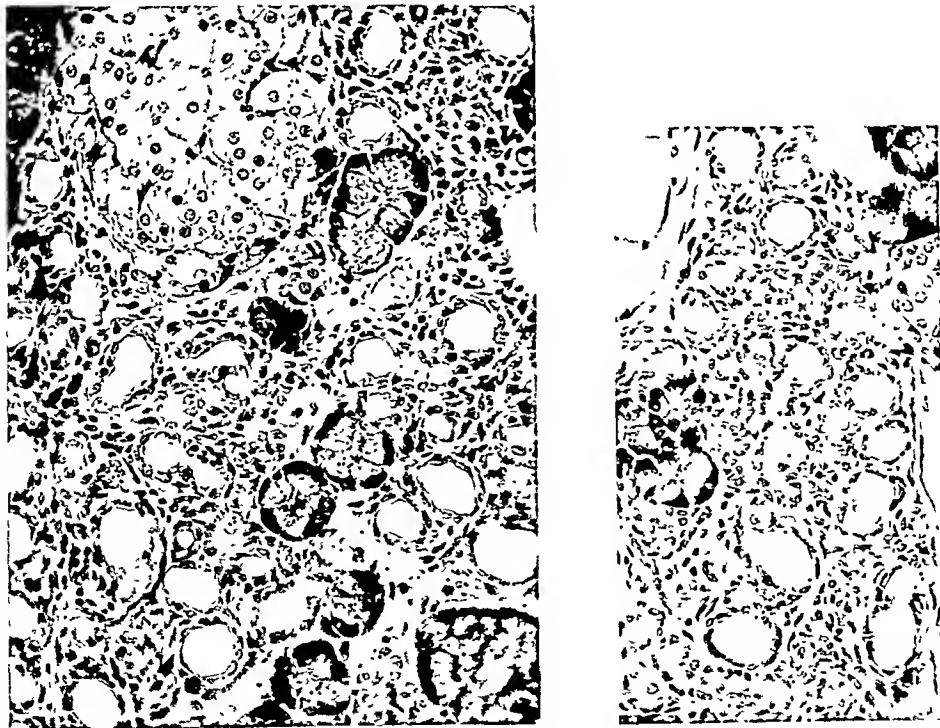
creas, although the degree of metaplasia was less pronounced than that in most of the treated rats.

As compared with the control rats, the incidence of meta-hyperplastic structures was greater in the treated rats, except in experiments 4 and 5 (Table 3) in the case of the thymus and liver.

This is obvious in experiment 1. In experiments 2 and 3 (Table 2), the incidence of all structures in all tabulated organs was about 65 per cent in the control rats and about 112 per cent in the treated animals. The respective figures in the experiments 4 and 5 (Table 3) were 77 and 120 per cent.

The incidence of structures in the thyroid, parathyroids, adrenals, and pancreas in experiments 2 and 3 (Table 2) was about 12 per cent in the control rats and 28 per cent in the treated animals. The respective figures for experiments 4 and 5 (Table 3) were about 27 and 50 per cent.

The most important fact, however, is



FIGS. 24 and 25. *Castrated male rat treated with testosterone propionate. Two different parts of the same structure, with the formation of follicles from the smallest pancreatic ducts. An island of Langerhans in the upper left in Fig. 24. In both figures, small solid nests of structural cells originated from the neoplastic follicles. ($\times 225$.)*



FIG. 26. Normal male rat treated with oestradiol benzoate-butyrate. A structure, in a state of formation from the ducts, developing between groups of acini (darkly stained) of normal pancreatic tissue. Formation of cystlike dilatations in some structural follicles. ($\times 140$.)

that none of the control rats had the severest degree of meta-hyperplasia, namely, adenomas; none of them had even such large adenoma-like structures as those that occurred in some of the treated rats. In the microphotographs are shown the largest structures found among those present in control rats. Comparison of these with those obtained in the treated rats clearly demonstrates this statement.

Also, in none of the control rats was disorganisation of cellular growth as great, e.g., as that shown in Figs. 11, 12, 14, 20, 22, and 23. These data indicate that the incidence of meta-hyperplastic structures, or their greater development up to the stages of adenoma-like structures or even true adenomas, were stimulated by the hormones used.

In the previous experiments on younger female rats,¹³⁻¹⁶ both in the control animals and in those treated with hormones, the meta-hyperplastic structures were not found

in the thyroid, parathyroid, adrenals, pancreas, and liver. They were observed in the thymus only. In the present experiments on younger rats (Table 1), they were not recorded in the control intact animals, and in the treated groups they were in most cases only slightly developed.

In addition, it is necessary to emphasise that the previous investigators referred to in this paper also found the meta-hyperplastic structures and tumours mostly in senescent or senile rats.

All these data indicate that in producing meta-hyperplastic structures, in particular adenomas, the co-operation of two factors might be instrumental, namely, the processes of ageing and overstimulation by hormones.

It is reasonable to suggest that even in those younger animals in which these structures rarely appear, the same co-operation might be in effect, since ageing might be premature, while the hormonal hypersecretion of one or more endocrine glands might start spontaneously.

The mechanism of co-operative effects of the processes of ageing and hormonal overstimulation in producing meta-hyperplastic growths can be explained by the following hypothesis. With ageing in the organism, several functions are weakening, including probably the mechanism regulating the normal cell growth in organs and tissues.

This results in the appearance of the nests of meta-hyperplasias in certain organs. These nests might remain quiescent and therefore harmless. Various stimulating factors, however, e.g., hormones, might promote their growth and transformation into tumours.

As was shown previously in our experiments on rats,¹³⁻¹⁷ the hormones produced a normal hyperplasia, or hypertrophy of cells, or both, in some organs. In this way, the hormones reversed the relative weight and also some histological features in these organs to the level observed at a younger age.

In the present experiments, however, simultaneously with these changes in nor-



FIG. 27. Control normal male rat. Adenoma-like structure of pancreas, of small size, usually found in those control rats that had these structures. ($\times 45$.) FIG. 28. Normal female rat treated with androstosterone. Large size of the structure found in most treated male and female rats. In both figures the normal pancreatic tissue is darkly stained, the structure lightly stained. FIG. 29. Control normal female rat. A gigantic island of Langerhans only exceptionally found in normal untreated rats. ($\times 63$.) FIG. 30. Normal male rat treated with thyroid hormone. At the same magnification as in Fig. 29, meta-hyperplasia of the island of Langerhans. ($\times 63$.) FIGS. 31 and 32. The same islands of Langerhans that were given at a small magnification in Figs. 29 and 30 shown at $\times 140$. Considerable difference in cellular and nuclear structure between the gigantic normal and the meta-hyperplastic islands.



FIG. 33. Normal male rat treated with oestradiol benzoate-butyrate. Epithelial adenoma-like structure (with light vesicular nuclei) spreading in and replacing the normal thymic tissue (small dark nuclei). ($\times 63$.)



FIG. 34. The same rat and structure as in Fig. 33. At $\times 140$, different structure of normal and neoplastic tissue is well defined.



FIG. 35. Normal male rat treated with oestradiol benzoate-butyrate. Solid thymoma (lightly stained) between normal thymic tissue (darkly stained) at the top (small remnant) and that at the bottom. ($\times 63$.)



FIG. 36. The same rat and thymoma as in Fig. 35 at $\times 140$. Structure of the cells is the same as in Fig. 31. Formation of small cysts (in the centre). On left, a narrow strip of normal thymic tissue sharply separated from the thymoma.

SUMMARY

1. Five experiments were performed on 201 female and 189 male rats, the age of which in different experiments varied from 17 to 27 months. Half the male rats were castrated about a month before the beginning of the experiment.

2. The appearance and development of meta-hyperplasias, adenoma-like structures or adenomas were studied both in the control rats and those treated with sex, thyroid, and anterior hypophysis hormones, and desoxycorticosterone acetate.

3. From the age of about 20 months on in some of the untreated rats of the breed used, a spontaneous development of meta-hyperplastic structures was found in the thyroid, adrenals, pancreas, thymus, and liver. In no case, however, did they become adenomas.

4. The hormones used increased in various degrees the incidence and development of meta-hyperplastic processes in the treated rats up to the stages of comparatively large adenoma-like structures or true adenomas, not observed in the untreated animals. Adenomas were found in some of the treated rats in the thyroid, parathyroid,

FIG. 37. Normal male rat treated with thyroid hormone. Meta-hyperplastic structure in the fasciculata zone of the adrenal with a haemorrhagic cyst. At the bottom, medulla (light). ($\times 83$.)

mal tissues, the growth of the meta-hyperplastic nests was also stimulated. In this way, and because of this, they developed into adenomatous tumours or adenoma-like structures. Possibly another additional factor might be instrumental in the above mentioned tumourogenic mechanism; namely, in old age the physiological brakes of growth are fully operating. Artificial overstimulation of growth processes, produced by hormones, operating simultaneously with the depressing action of the natural growth brakes, might easily produce or increase the disorganisation of local growths. In this way, tumourogenic, in particular a malignant, effect might be intensified.

Of course, the suggestions made do not exclude the possibility that in the production of adenomas other causes and mechanisms might be instrumental.

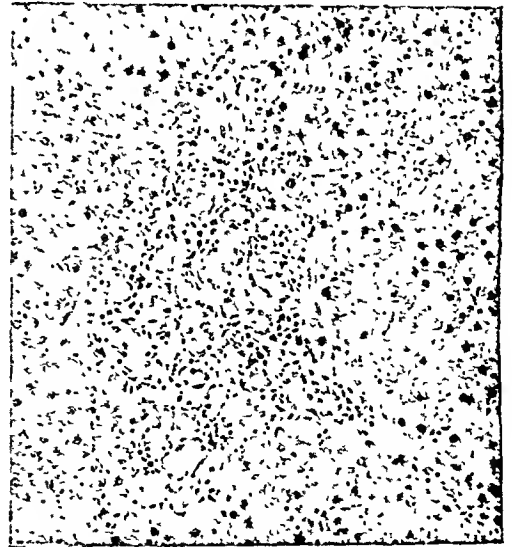


FIG. 38. Control normal male rat. Follicular meta-hyperplasia of smallest bile ducts in the liver. Structure of a larger size, sometimes found in control rats. Usually the nests are smaller. ($\times 140$.)

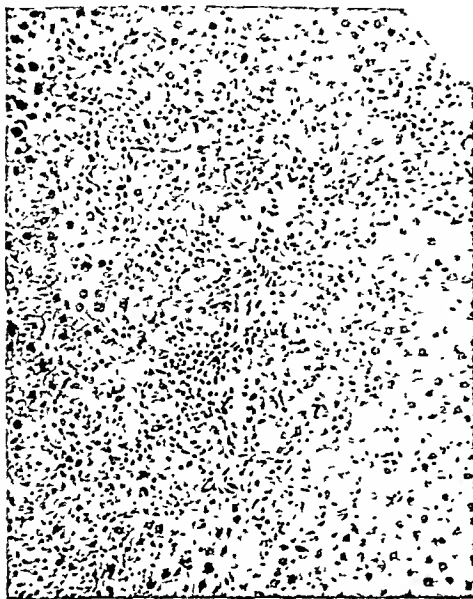


FIG. 39. Control castrated male rat. This structure is exceptionally large for control rats, and it was found in one control rat only. ($\times 140$.)

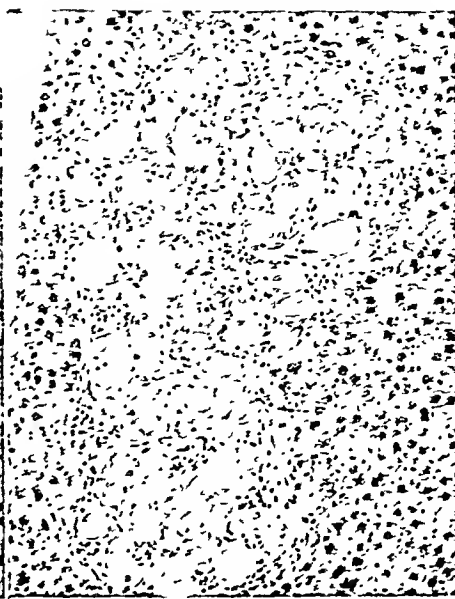


FIG. 40. Normal male rat treated with oestradiol benzoate-butyrate. Size of the structure more typical for the rats treated with hormones. ($\times 140$.)

adrenals, and thymus, while comparatively pronounced adenoma-like structures were observed in the pancreas and liver.

5. The various forms of the structures observed in different rats showed a gradual transition, through many intermediate stages, of simple meta-hyperplastic nests of few cells into large adenomas with disorganised cell growth and form.

6. Thus, the present experiments confirm the fact that the smallest meta-hyperplastic nests of cells should be considered as the latent quiescent centres of neoplasms. Stimulating factors (as hormones in the present experiments) might initiate and promote the growth of these centres, transforming them into adenomas and, probably, carcinomas.

7. Therefore, a detailed investigation of the causes producing these minute epithelial meta-hyperplastic nests and the mecha-

nism of their development in various organs appears to be of great importance.

8. Probably, as in the case of mice, not all the strains of rats are susceptible to tumour development. It would be important to study whether these minute quiescent nests are also present in the resistant strains.

9. The number of rats in the different groups was considered not sufficient to make a comparative assay of the adenomagenic action of each of the hormones, or their combinations, used in the present experiments.

10. The results obtained, however, indicate that there is a co-operative activity of ageing processes and hormonal overstimulation in producing or enhancing meta-hyperplastic structures. The possible explanation of the mechanism of this co-operative adenomagenic activity was suggested.

(For references see page 922.)

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for the work in 1938. Among the limitations of such early apparatus is the fixed vertical x-ray beam, so that the full advantages of supervoltage by accurate direction of multiple small beams or by rotational therapy could not be exploited. In quality, the therapy beam has about the same effective wave length (0.025 Å) as that of more modern 1000 kv. apparatus, but the heavy filter required (4.5 mm. Pb) entailed some sacrifice of output (approx. 20 r/min. at 100 cm F.S.D.).

The physical advantages of supervoltage x-rays are (1) increased penetration, (2) improved skin tolerance, (3) restriction of the radiation to the geometric beam, with consequent reduction in systemic radiation reactions, and possibly (4) a differential tissue tolerance.

The main emphasis of the book is on the "clinical management of cancer by roentgentherapy as taught by Coutard," and it contains a wealth of valuable observations, detailed case histories, and informative illustrations that are equally pertinent to any type of radiotherapy from 40 kv. to 40 Mev. The authors consider that supervoltage therapy is a desirable part of a cancer treatment center, in that it has definite indications in certain forms of cancer and has advantages over lower voltages in other types; but they do not clearly summarize these indications and advantages—the reader is left to deduce them from the clinical material presented.

They find supervoltage therapy advantageous for advanced cancers of the lip, oral cavity, and pharynx, particularly for those arising in the base of the tongue; their experience with cancers of the larynx and of the maxillary sinus leads them to conclude that the type of cancer rather than the voltage of the roentgentherapy determines the result. In cancer of the esophagus, treatment with supervoltage is better tolerated than with medium voltage, and "deserves a more thorough trial than it has so far had." In cancer of the bladder (10 patients well for 5 yrs. or more of 64 treated), they think that only those papillary carcinomas that have not invaded the bladder muscle are curable by external roentgentherapy, but they "are not prepared to give an opinion as to the superiority of supervoltage." Breast cancer as a whole they find invulnerable to ionizing radiation, the lymph-node metastases still more so than the primary growth, and "these are fundamental problems of radiobiology . . . the answers will not be found by increasing the energy of the radiation." In carcinoma of the cervix uteri, they are "pessimistic that further technical improvements will be made" that will cure more cases.

The authors are thus not merely conservative, but they think that radiotherapy has reached a stage where it cannot look for any great advance comparable to that given it by Regaud, Lacassagne, and Coutard. Time has a way of falsifying predictions of this sort, especially when based on the outlook of one school to the exclusion of others working in the same field. Nevertheless, this is an excellent book from which every radiotherapist can profit—the only misleading thing in it is its title.—*R. Phillips, M.B. (Lon.)*

RADIOACTIVE ISOTOPES

Brues, Austin M. [Argonne Nat. Lab., Chicago, Ill.]: **Biological hazards and toxicity of radioactive isotopes.** J. Clin. Investigation 28: 1286-1296, Nov., 1949.—The clinical use of radioisotopes requires careful consideration of their human toxicity, both from the point of view of the patient and the staff. The hazards of acute overdosage must be evaluated, but more particularly the hazards of chronic radioelement poisoning must be considered, particularly with elements of long half-life. At the present time, in the human, we have detailed knowledge of the consequences of deposition only in the case of Ra. For other radioisotopes, extrapolation from animal data must be made.

The acute reaction from isotope toxicity is called acute radiation sickness and is seen usually when the tissue radiation is homogenous and approaches the lethal dosage. This may be expected to be seen following administration of large quantities of Na^{24} and P^{32} . In the animal, it has been seen also after the injection of a purely bone seeking isotope, such as Sr^{90} . Subacute radiation reactions show aplastic anemia as a predominant feature and may be expected to be seen following external x- or gamma radiation that has been given intermittently or continuously over a long period or following the injection of a radioisotope with sufficient half-life if the isotope is retained in high dosage. Late or chronic radiation changes may be expected to result from the deposition of small quantities of long-lived radioisotopes. In the human, Ra has resulted in bone sarcoma when the retained dose is in the order of 1 µg. Experimentally, carcinogenesis has been seen in animals both when long-lived isotopes have been deposited for a long time and following single doses of radioisotopes that were then excreted provided the period of observation was long. No clear information is available regarding the dose-time relationships required for carcinogenesis. In other words, the recovery factor is unknown.

The maximum permissible dose for daily x-ray exposure has recently been set at 0.3 r per week. For internally deposited Ra, the permissible retained amount has been set at 0.1 µc. Permissible levels for radioisotope exposure, at the present, must be derived from these 2 figures.

The author feels that, under the following conditions, it may be justifiable to exceed these permissible levels:

1. Clinical investigation and diagnostic procedures: Arguing from the precedent of diagnostic radiography, it would appear that a total dosage of beta and gamma emitters between 1 and 10 rep to the tissue most exposed may be justified if not repeated in the case of isotopes of short half-life whose metabolic fate is well understood. Na^{24} , K^{42} , I^{131} , and possibly P^{32} are included as examples. It is pointed out that improvements in technique may result in extending the area of safe use of radioisotopes in this category.

2. Treatment of disease where other therapy is available: Since changes are being sought, doses

must necessarily be far above the permissible level. The principle of calculated risk is paramount, as it is in all medicine. It is emphasized here that the fact that the consequences of such treatment may be long delayed must be kept in mind.

3. Treatment of hopeless malignant disease: Here it would seem justifiable to use whatever means offers some chance of palliation or cure or of gaining information to that end, where this can be done without detriment to the patient. It is essential that all cases be selected on the basis of inoperability and also that the cases be chosen (1) as a result of a biopsy from a metastatic lesion or primary lesion deemed inoperable and (2) after consultation with a specialist in this field.

Data are then presented on the toxicity of bone-seeking elements that indicate that for both monthly and single treatment with Sr^{90} a definite calculable increased probability of the appearance of tumors in these animals is produced, presumably by the injection. It is not known at present whether a threshold exists for such effects.—*J. J. Nickson, M.D.*

BREAST

Guttmann, Ruth J. [Memorial Center, New York City]: X-ray therapy of primary inoperable carcinoma of the breast. *Radiology* 51: 567-571, Apr., 1950.—Since 1910, 82 cases of primary inoperable carcinoma of the breast were proved by biopsy and treated exclusively with x-ray therapy at Memorial Hospital. The treatment was directed to the tumor in the breast as well as to the lymphatics in the supra- and infraclavicular regions and in the axilla itself. In the presence of skin metastases or in an inflammatory type of cancer, radiation to the surrounding chest wall was added, in the attempt to seal off the disease. As many portals as possible were used in order to cover the involved region with a wide margin of safety. The factors used were 250 kv., 1.5 mm. Cu, 50 cm. TSD. The daily dose was 250 r measured in air, corresponding to 310 r measured in the center of the field. The total dose was 2500 to 3000 r measured in air per field. The tumor doses varied between 3000 and 4000 r at the center of the tumor (1 patient received not more than 2000 r to this area). The factors used in the treatment of the chest wall were: 120 kv., 3 mm. Al, 30 cm. TSD. The single exposure was 100 r measured in air, the total dosage to each field between 2400 and 2800 r measured in air. The course of the treatment lasted between 4 and 8 wks., dependent on the number of fields used. The irradiation was well tolerated, especially with the use of vitamin B., which was given in regular dosages of 50 mg. 3 times daily. The skin was kept dry and only mild powders were used. The aftereffects observed were (1) skin changes with fibrosis and telangiectases but no radiation ulcer, (2) fibrosis of muscles and fat, resulting in swelling and limitation of function of the arm, (3) pneumonitis and lung fibrosis with dyspnea, reaching its peak 10 to 12 mos. after therapy, usually decreasing afterwards.

A striking result was noticed in most cases of ulcerated inoperable carcinoma, though many of

No. patients	Surv. more than yrs.	No. surv. with no evid. disease
2	8	2
4	7	4
5	6	4
9	5	4
11	3	9
26	2	10
60		

these patients had been refused treatments elsewhere "because they were too advanced." A statistical analysis of these 82 cases is impossible because the time of observation is too short. However, since a survival for 2 or more yrs. in activity and comfort is certainly worth while, the following figures seem justified. Of this group, 15 patients died during the 1st yr.; 7 of the remaining 67 patients have been treated since 1947, which leaves 60 patients living 2 or more yrs. This group included patients of all ages; the youngest 27 yrs. old, the oldest, 82 yrs., the majority, between 40 and 65 yrs. old. No prediction of the response of these patients to irradiation could be made by evaluation of data contained in their charts. Of the 2 patients surviving more than 8 yrs., 1 received a tumor dose of only 2000 r. This patient was 27 yrs. of age and was first seen 3 wks. after delivery with multiple lesions in both breasts and various bones. Histological examination revealed a highly malignant carcinoma. Our tumor dosages were usually relatively small and were not quoted with the intention of starting a controversy over the necessary tumor dosages, but only to bring out the fact that good results can be achieved even when we may be forced to limit the tumor dose to an unusually small amount.

In the hands of a selected group of exceptionally skilled men, the field of surgical treatment of cancer has been broadened, and, if a cure cannot be achieved, the extension of the life span of a patient for several months is considered a worthwhile result. But for these inoperable patients, surgery has nothing to offer. X ray therapy, when properly planned, cannot do any harm; it was intended, therefore, to give proof that this method should be attempted in all patients with primary inoperable carcinoma of the breast in order to make their existence more tolerable and sometimes to restore them to a normal life.—*R. J. Guttmann, M.D.*

DIGESTIVE TRACT

ORAL CAVITY

Sarnat, Bernard G., & Schour, Isaac: *Oral and Facial Cancer*. Chicago. Year Book Publishers, Inc. 1950. 300 pp. \$6.00.—The authors have recognized the necessity for a monograph on mouth cancer and have attempted to prepare one for both the medical and dental practitioner in one volume. The book is well written and profusely illustrated with clinical photographs and line

drawings. The pedagogical techniques employed are effective and attractive. In the reviewer's opinion, the monograph would be more informative as a teaching instrument for practitioners (both dental and medical) if its scope did not include cancer of the skin of the face, cancer of the salivary glands, and tumors of the mandible and maxilla, and the emphasis were placed only upon cancer of the oral cavity. Furthermore, the inclusion of sections on treatment in many of the chapters (radiation therapy vs. surgery) detracts from the effectiveness of the book as a teaching tool, since the subject of therapy for cases of mouth cancer is complicated, even in the hands of the specialist. The role of dental trauma in the causation of mouth cancer is overemphasized.—*H. E. E.*

Sharp, George S.; Williams, Herbert F., & Pugh, Robert E., Jr. [Pasadena, Calif.]: *Irradiation as the preferred treatment of cancer of the lip*. *J. A. M. A.* 142: 698-707, Mar. 11, 1950.—Cancer of the lip may be cured by either surgery or irradiation. The authors believe that a better cosmetic result is obtained with radiation therapy. Calculation of tissue dosage at the tumor site is one of the most important factors in obtaining a good therapeutic result with radiation. The principle of irradiating the smallest volume of tissue consistent with eradication of the lesion was employed in 208 proved cases (from 1932 to 1943, inclusive). The efficacy of surface Ra, alone or combined with interstitial radiation, is pointed out. The 5-yr. cure in this series of cases is 84.2%.

Cervical metastasis developed at some time during the course of the disease in 8.6% of the cases; the 5-yr.-cure rate in this group is 61% (treated by neck dissection).—*H. E. E.*

Spreng, Max; Casser, Fritz, & Oppikofer, Ernst: *Zahnärztliche Prothese und Mundhöhlen-Carcinom. Odonto-Stomatologie, Vol. 1. [Dental Prostheses and Carcinoma of the Oral Cavity. Odontostomatology, Vol. 1.]* Basel. Verlag Birkhauser. 1949. 192 pp. 23.50 Swiss francs.—The authors of this book have utilized the material observed by them at the University of Basel to present oral cancer in its various phases. They have listed and illustrated with excellent photomicrographs and photographs the precancerous, early cancerous, and late cancerous lesions of the oral cavity.

The role of chronic irritation resulting from ill-fitting dentures is stressed. The use of suction cups on full upper dentures is rarely noted today in the United States, but the evidence of poorly fitting and poorly designed partial dentures as contributory causes of oral cancer is well documented.

The necessity for regular observation and alertness by the physician and dentist for the detection of precancerous and early cancerous lesions is emphasized.—*A. R. Shepard, D.D.S.*

SALIVARY GLANDS

Hevenor, Engel P., & Clark, Charles E. [St. Luke's Hosp., New York City, & Rhode Island Hosp., Providence]: *Adenolymphoma (papillary*

eyctadenoma lymphomatosum). *Surg., Gynec. & Obst.* 90: 746-751, June 1950.—Twenty cases are reported. The authors believe that this tumor has its origin from ectopic pharyngeal or eustachian-tube endoderm. Surgical excision is the treatment of choice and was performed in 19 cases; in 7, no follow-up was obtained. The remaining 13 have been followed from 1 mo. to 12 yrs. with no recurrences reported. 1 case of adenolymphoma of the hypopharynx is reported. [No well-documented case of adenolymphoma arising in minor salivary-gland tissue has ever been reported in the literature. It is possible that adenolymphoma arising in the submaxillary salivary gland may extend centrally to reach the pharyngeal wall, and thus present as a hypopharyngeal tumor.]—*H. E. E.*

Kidd, H. A. [St. Helier Hosp., Eng.]: *Complete excision of the parotid gland with preservation of the facial nerve*. *Brit. M. J.* 1: 989-991, Apr. 29, 1950.—Radical resection of the parotid gland is the method of choice for the treatment of mixed tumors. The main 7th nerve is sacrificed only in cancer cases. [Frequently the facial nerve can be dissected out and preserved if it is not involved by tumor.] A surgical technique is described that allows wide removal of the parotid gland with preservation of the facial nerve and its branches. The cervical branch in the submaxillary triangle is found first and traced backward to where it joins the main nerve at the stylomastoid foramen. The entire plexus is then dissected out. [Some surgeons prefer to identify the main 7th nerve at the stylomastoid foramen first and then proceed to dissect out the branches.] 9 cases are reported in which the operation was successfully performed; average operating time was 2-3 hrs.—*H. E. E.*

STOMACH

Dawson, J., & Richards, H. G. Howell [Roy. Hampshire County Hosp., Winchester, Eng.]: *Carcinoma in a herniated gastric cardia associated with short oesophagus*. *Brit. J. Radiol.* 23: 270-273, May, 1950.—Association of carcinoma of a herniated gastric cardia with a short esophagus is apparently rare. The patient was a 76-yr.-old woman seen in October, 1948. A papillomatous adenocarcinoma and a hiatus hernia of the stomach were found at the time. The patient refused operation. She was readmitted in March, 1949. At operation, an ulcerated carcinoma involving the lower end of the esophagus at its junction with the cardia was found. Histologically, the tumor was a poorly differentiated adenocarcinoma of the cardio-esophageal junction. 2 types of cell pattern were intermixed: (1) large neoplastic columnar-cell acini and (2) small, poorly formed mucus-producing acini. The patient died shortly after operation; permission for autopsy was not obtained. The complete diagnosis *in vivo* was made by the co-ordination of radiological, esophagoscopic, and histological findings. 4 theoretical possibilities with respect to etiology are presented. None of them is established, largely owing to the lack of material and of autopsy findings in cases such as this.—*P. de R. Kolisch, M.D.*

Smithers, D. Waldron [Roy. Cancer Hosp., London, Eng.]: The association of cancer of the gastric cardia with partial thoracic stomach, short oesophagus and peptic ulceration. *Brit. J. Radiol.* 23: 261-269, May, 1950.—These 4 cases with a case reported by Rennie and Land and a case reported concurrently by Dawson and Richards, bring to a total of 12 the cases of cancer of the gastric cardia associated with short esophagus in which histological reports are available. Three possible reasons for the development of cancer in these cases are given: (1) that the association is fortuitous, which seems unlikely although data are not now sufficient to be conclusive; (2) that the sequence of events, lax hiatus, contraction of the esophagus, hiatal hernia, reflex flow of gastric juice, which leads to esophagitis and peptic ulceration, predisposes to the development of cancer; (3) that cancer of the region of the cardia is one of those upper abdominal lesions that may lead to reflex contraction and shortening of the esophagus, so that the tendency for these tumors to become intrathoracic is accentuated in those patients who already have a lax hiatus. [The last is the explanation preferred by the author, although he concedes other possibilities.]

If the tumor were the result of chronic esophagitis, a predominance of squamous-cell carcinomas might be expected, whereas if spasmotic contraction were a sequel to the presence of tumor, adenocarcinoma might be expected to predominate. Among the 10 cases discussed in this paper, there were 7 adenocarcinomas, 2 squamous-cell carcinomas, and 1 leiomyosarcoma.—*P. de R. Kolisch, M.D.*

Weinberg, Joseph, & Greaney, E. M. [Veterans Adm. Hosp., Van Nuys, Calif.]: Identification of regional lymph nodes by means of a vital staining dye during surgery of gastric cancer. *Surg., Gynec. & Obst.* 90: 561-567, May, 1950.—A method of staining the regional lymph nodes of the stomach to facilitate their identification and surgical extirpation is presented. 5 cc. of 2% pontamine sky-blue dye is injected into the anterior aspect of the stomach along the lesser and greater curvatures as soon as the abdomen is opened. The surgical procedure is delayed for 15 min. to permit passage of the dye into the lymphatics. The technique results in easy visualization of the regional nodes and permits accurate and adequate removal of the node-bearing tissue. Addition of hyaluronidase to the dye appears to accelerate the diffusion process. It is of more than incidental interest that the authors regard total gastrectomy, together with removal of the spleen and greater and lesser omenta, as the procedure of choice for the curative treatment of resectable gastric cancer. Subtotal resection is reserved for those cases that are regarded as incurable or for patients whose general condition is so poor as to make the more radical procedure too hazardous.—*L. H. Guiss, M.D.*

COLON AND RECTUM

Boehme, Earl J. [Santa Monica Hosp., Calif.]: The surgical treatment of familial polyposis of the colon; a report of seven cases, six in one

family. *Ann. Surg.* 131: 519-533, Apr., 1950.—The author presents in detail 7 patients (6 in 1 family, ages 12 to 48 yrs.) having extensive familial polyposis of the colon. The disadvantages of multiple stage operations for this condition are discussed, and the advantages of 1-stage total colectomy with primary end-to-end anastomosis of the ileum to the upper rectum or lower sigmoid emphasized. All patients had this 1-stage colectomy, though 1 with a suspicious lesion in the rectum at the 1st operation later had proctectomy for early invasive carcinoma. All patients have no more than 2 or 3 stools daily.

The author deplors ileostomy for this condition and preserves the rectum except when cancer is present in that segment. A new method of suction canterv introduced here allows destruction of as many as 300 polyps at one sitting without anesthesia. The polyp is held away from the bowel wall and the smoke is instantly removed while the polyp is being accurately fulgurated. The method avoids the scarring, pain, and occasional perforation characteristic of the conventional ball-point canterv.

All patients have an annual inspection of the rectal segment to the point of the anastomosis with the ileum. The very few small polyps appearing in the rectal segments have been fulgurated, keeping the rectum free from polyps and any possibility of malignant change.—*E. J. Boehme, M.D.*

Grinnell, Robert S. [Columbia Univ., Coll. Phys. & Surgeons, New York City]: Lymphatic metastases of carcinoma of the colon and rectum. *Ann. Surg.* 131: 191-506, Apr., 1950.—The lymph-node metastases in 322 specimens of carcinoma of the colon and rectum removed at operation and cleared by the Spalteholz technique were studied. The locations of the nodes were charted on drawings to show their relationship to the tumor and the blood vessels. Metastases were found in 13% of the colonic and 53% of the rectal tumors. When the main lymphatic route was blocked by node metastases, in the colon specimens, lateral and sometimes retrograde spread occurred along the paracolic lymphatics in 7% of the specimens or in 12% with node metastases. Wider resection of both bowel and mesentery is accordingly advocated for tumors of the transverse and left colon. Involvement of the most proximal node along the main lymphatic route (Dukes's classification C2) was found in 27 specimens from the colon, 3 from the rectosigmoid, and 13 abdominoperineal specimens from the rectum, representing a removal incidence of 16, 9, and 12%, respectively. Higher ligation of the inferior mesenteric artery and removal of its accompanying nodes in certain tumors of the left colon is therefore suggested, making use of the descending branch of the left colic artery to supply the proximal limb of the anastomosis, or even of the middle colic artery by anastomosing the distal transverse or upper descending colon to the lower sigmoid or upper rectum. It is suggested that the operation of anterior resection and anastomosis with ligation of the inferior mesenteric vessels be extended upward to include tumors of the sigmoid and that the vessels be ligated as high

as possible, even above the left colic artery in certain cases. In abdominoperineal resection for carcinoma of the rectum, it is also suggested that the inferior mesenteric artery be ligated at its origin above the left colic branch and that the colostomy be done in the transverse or descending colon.—*R. S. Grinnell, M.D.*

Heller, Elwyn L., & Lewis, Homer H., Jr. [Univ. Pittsburgh, Pa.]: **Benign lymphoma of rectum.** *Am. J. Path.* 26: 463-471, May, 1950.—Nine cases of benign lymphoma of the rectum are reported with no evidence of disease elsewhere in the lymphatic tissue. It is significant that the authors emphasize the benignancy of this lesion in spite of features that simulate malignant proliferation. These features are discussed under three headings, namely, destruction of the muscularis mucosae, absence of capsule, and diffusion of lymphoblastic cells beyond the confines of the follicles.

The tumors vary from a few mm. to 8 cm. in diameter, usually are solitary, and the majority are polypoid but occasionally intramural nodulation is found. There is no site of predilection noted in the rectum, and the lesion has been reported in the colon above the rectum.

[It is stated that the clinical course established the benign character of the lesion, but in view of follow-up examinations reported on only 5 of the 9 cases, these varying from 2 to 15 mos., any conclusions drawn would seem to be speculative.]—*K. P. Knudtson, M.D.*

PANCREAS

Howard, John M.; Moss, N. Henry, & Rhoads, Jonathan E. [Univ. Pennsylvania, Philadelphia]: **Hyperinsulinism and islet cell tumors of the pancreas with 398 recorded tumors.** *Internat. Abstr. Surg.* 90: 417-455, May, 1950.—A collective review of 398 tumors is presented, data being based on 10 patients explored at the Hospital of the University of Pennsylvania, 23 cases of islet-cell tumors found at autopsy in its Department of Pathology, and the remainder collected from the literature. The 3 pathological classifications used were: benign adenomas, "suspiciously malignant tumors" (defined as appearing histologically malignant but clinically benign), and islet-cell carcinomas.

Cases	Functioning	Non-functioning	Not stated	Total
Benign Adenoma	200	85	28	313
"Suspiciously Malignant"	42	6		48
Carcinoma	22	12	3	37
TOTAL	264	102	31	398

Clinical diagnosis of a functional islet-cell tumor was based on: (1) signs and symptoms of insulin shock; (2) repeated fasting-blood-sugar concentrations less than 50 mg.; (3) relief of symptoms by glucose administration; (4) lack of relief by low carbohydrate diet to exclude functional hypoglycemia.

200 patients with a localized tumor were submit-

ted to surgery with an over-all mortality of 8.4%. Excluding operative mortalities 87.3% were relieved of their hypoglycemia. When the tumor can be found, simple enucleation is the procedure of choice, otherwise subtotal resection of the pancreas may be done, although only about one half of patients so treated will be benefited. This is due to the fact that the tumors are about evenly distributed throughout the substance of the gland. The results of treatment of islet-cell carcinoma are discouraging, only 1 of 37 patients being alive for a period of 4 years.—*L. W. Guiss, M.D.*

ENDOCRINE ORGANS

Bartels, Elmer C., & Cattell, Richard B. [Lahey Clin., Boston, Mass.]: **Pheochromocytoma: its diagnosis and treatment.** *Ann. Surg.* 131: 903-916, June, 1950.—A suspicion of pheochromocytoma is justified in any patient with vasomotor attacks who has such associated symptoms as excess sweating with blotchiness of the skin, toxemia during the early months of pregnancy, findings of fluctuant or sustained hypertension, in whom a suspicion of hyperthyroidism is present.

The salient laboratory findings aiding in the diagnosis of pheochromocytoma are elevation of the metabolic rate without goiter, abnormal pyelograms (such as displaced kidney or calcification), and elevated blood sugar or a diabetic glucose tolerance test.

Certain incitatory substances such as histamine, mecholyl, or etamon are helpful in making the diagnosis of pheochromocytoma. These tests, however, are not specific and must be carefully carried out for proper interpretation. Dibenzamine and benzodioxane also are helpful in those patients with pheochromocytoma who have sustained hypertension, but sufficient experience has not proved their safety.

The chief danger from surgical removal of a pheochromocytoma is a severe hypertensive reaction with subsequent acute left heart failure. This danger can probably be avoided by using an adrenergic agent during the operation. More experience is necessary before these drugs can be intelligently utilized.

Removal of the tumor leads to cure unless the tumor (pheochromocytoma) is malignant and leads to metastatic disease or has already produced serious vascular damage.—*L. C. Bartels, M.D.*

Eisenberg, Stuart J., & Sahyoun, Philip F. [M. Coll. Virginia, Richmond]: **Mixed tumors of the thymus; criteria for their differentiation and their radiotherapeutic response.** *Arch. Path.* 49: 404-417, Apr., 1950.—Clinical summaries and histological descriptions of surgical or autopsy material from 7 cases of mixed tumor of the thymus are presented. 6 died in 1 to 6 yrs. after onset of symptoms, while the 7th was last seen in poor physical condition 10 mos. after symptoms appeared. The entities of thymic carcinoma and thymic lymphosarcoma are generally accepted, but the concept of mixed tumors arising from the thy-

mus is said to have received less attention. During a study of Hodgkin's disease, these 7 cases, not conforming to the standard patterns of that disorder, were uncovered. Each showed a mediastinal mass, with course and irradiation response not in accord with those of Hodgkin's disease. The differential histological features of mixed tumor of the thymus are: the reticular epithelial sheets, the enormous tumor giant cells and the tendency toward concentric fibrosis, and the formation of aborted Hassall's corpuscles. In general, it can be said that the course is more prolonged than that of the average case of Hodgkin's disease. Whereas, in Hodgkin's disease, the involvement of the nodes and the tumor disappear completely after radiation, in the mixed tumors of the thymus there are arrest and improvement but not complete regression. In Hodgkin's disease, the lesions occur in pre-existent lymphoid tissue, but the mixed tumors of the thymus have a tendency to behave like carcinoma and infiltrate the adjacent organs, namely, mediastinal structures and lungs. The course and the therapeutic responses observed in these 7 cases suggest the superiority of x-ray radiation over nitrogen mustard in control and palliation.—*I. G. Fowler, M.D.*

Love, J. Grafton, & Marshall, Thomas M. [Mayo Clin., Rochester, Minn.]: **Craniopharyngiomas (pituitary adamantinomas).** *Surg., Gynec. & Obst.* 90: 591-601, May, 1950.—The subject of craniopharyngioma is reviewed on the basis of 100 proved cases observed at the Mayo Clinic and a review of the literature. The developmental anatomical aspects of the subject are presented and, after consideration of all available evidence, the authors conclude that the term "pituitary adamantinoma" is the logical one for this tumor. [Other terms that have been employed are hypophyseal-duct tumor, craniopharyngeal-duct tumor, Rathke-pouch tumor, craniobuccal cyst, supracellar cyst, epithelioma, and interpeduncular cyst.] The histological similarity of these tumors to the embryonic enamel organ is striking.

Pituitary adamantinoma comprises 4% of all intracranial neoplasms and about 30% of all pituitary tumors. It is the most frequently occurring tumor of the supratentorial cavity in children. The tumor produces a multitude of symptoms resulting mainly from a disturbance of pituitary function, pressure upon the optic chiasma, and hydrocephalus. Headache and vomiting are the most frequent early symptoms. The diagnostic aspects of the problem (objective neurological findings, visual-field and x-ray studies, etc.) are discussed in detail. Roentgenologically, calcification of the tumor was noted in 56% of the cases in the present series.

Although complete surgical excision is the ideal method of treatment and most certain to cure, the presence of the adjacent vital structures makes such surgery difficult and frequently impossible. Aspiration of the contents of the tumor, followed by as complete removal of the capsule as is anatomically feasible, is apparently the most effective and least hazardous procedure.

The operative-mortality rate is high (40%) and

recurrences frequent (only 17 patients of 58 who survived surgery are alive 1 or more yrs. after surgery). Although pituitary adamantinoma is radioresistant [as is adamantinoma of the mandible and maxilla], the authors feel that some measure of palliation may be obtained with radiation in the occasional inoperable case since 10 in this series were benefited by pre- and/or postoperative radium or x-ray therapy.—*H. E. E.*

Rienhoff, William Francis, Jr. [Baltimore, Md.]: **The surgical treatment of hyperparathyroidism; with a report of 27 cases.** *Ann. Surg.* 131: 917-913; disc. 913-914, June, 1950.—A detailed clinical and anatomical analysis is made of 27 cases of hyperparathyroidism encountered at the Johns Hopkins Hospital (25 cases of benign adenoma, 1 of hyperplasia, and 1 of carcinoma of the parathyroids). The early recognition and successful treatment of this condition is important because in practically all patients irreversible and irremediable complications (renal and osseous) occur and persist, even after the hyperparathyroidism has been corrected. Tetany is a frequent and serious postoperative complication.

The operative correction of this disease requires considerable knowledge and skill. The surgeon must not only be able to distinguish adenoma from hypertrophy of the parathyroid glands but must also be prepared to explore the neck and superior mediastinum in the event exploration of the anterior and posterior aspects of the thyroid glands reveals no evidence of a parathyroid lesion.

The author introduces evidence to indicate that the determination of calcium in the spinal fluid may yet be established as a reliable diagnostic method to differentiate the hypercalcemia of hyperparathyroidism from other conditions in which hypercalcemia is present.—*H. E. E.*

FEMALE GENITAL TRACT

CERVIX AND UTERUS

Friedman, Herbert P., Jr. [Chicago Living-in Hosp., Ill.]: **The use of ultraviolet light and fluorescent dyes in the detection of uterine cancer by vaginal smear.** *Am. J. Obst. & Gynec.* 59: 852-859, Apr., 1950.—This is a preliminary report of a new technique as a screening method in the detection of uterine cancer in which the cytology of vaginal smears is studied microscopically by staining with fluorescent dyes (fluorochromes), using filtered ultraviolet light as a source of illumination. The simple and inexpensive apparatus and technique for fluorescence microscopy and fluorescence photomicrography are given.

Nentral berberine sulfate (Merck), acid fuchsin (National Aniline), and acridine yellow (Grubler) are the fluorochromes used in the staining procedure, which takes approximately 10 minutes to complete. Only dyes from these sources should be used. Cells so stained fluoresce brightly and clearly with well-defined nuclear and cytoplasmic detail against a black background when the stained slide is viewed in ultraviolet light through the ocular of the microscope.

Brief descriptions of the various distinguishing fluorescent colors associated with normal epithelial cells, leukocytes, erythrocytes, *Trichomonas vaginalis*, *Monilia*, and bacteria of the vaginal flora are mentioned. The use of this technique for differentiating normal from malignant cells by morphology, degree of fluorescent brilliance, and variation of nuclear and cytoplasmic fluorescent colors is cited.

This same technique can be used in the cytological study of bronchial aspirations, sputum, ascitic fluid, and pleural exudates.—*H. P. Friedman, Jr., M.D.*

Halpert, Béla [Houston, Tex.]; **Bennett, Henry G., Jr., & Hartford, Walter K.** [Univ. Oklahoma Sch. Med. & Hosps., Oklahoma City]: **Incipient squamous cell carcinoma of cervix uteri.** Arch. Path. 49: 555-562, May, 1950.—An incipient carcinoma of the cervix is not intraepithelial, is not noninvasive, and is not in situ. An incipient squamous-cell carcinoma of the cervix is defined as one in which the neoplastic squamous epithelial cells are on, or immediately beneath, the surface and the extension is limited to the tissues immediately subjacent to the surface. Incipient carcinoma of the cervix was proved histologically in 28 of 275 women—smear (abnormal cells in 15 of 19 cases), biopsy, operative specimen. Half of these patients had no complaints; the others cited vaginal bleeding. Macroscopically, all but 2 cervices showed a somewhat altered appearance, from slight focal red discoloration to more or less erosion of the external os. The lesions resembled a chronic inflammatory process rather than cancer. The data re-emphasize the detectability of cervical carcinoma in its incipient stage when clinical signs and symptoms are wanting and the lesion is still local.—*B. Halpert, M.D.*

Harnett, W. L. [Brit. Emp. Cancer Campaign]: **A statistical report on 955 cases of cancer of the cervix uteri and 321 cases of cancer of the corpus uteri.** Brit. J. Cancer 3: 433-473, Dec., 1949.—Hospitals in the Administrative County of London were surveyed by questionnaires. During the period 1938-1939, 17,203 cases of cancer were registered, of which 955 were cancer of the cervix and 321 of the corpus uteri. These patients have now been followed for 5 yrs. or more. Of the 859 cases of primary cancer of the cervix, 819 (95.3%) occurred in married women or in widows and 37 (4.3%) in single women; in 3 cases, the civil status was not known. The author concludes that there is a higher incidence of cancer of the cervix among married women and widows at every age than among single women; between the ages of 45 and 65, it is about 7 times as great. The probability of cancer of the corpus uteri is slightly greater among single women. A significantly greater proportion of single women less than 45 yrs. have cancer of the cervix than have cancer of the corpus. Of those more than 45 yrs., there is a corresponding deficiency of women with cancer of the cervix. Among married women and widows, there is also a greater proportion of cases of cancer of the cervix in women less than 45; of those more than 65 yrs., the proportion with cancer of the corpus is significantly

greater. In neither cancer of the cervix nor of the corpus does the family history of cancer appear to be significant. Compared with cancer of the cervix, 11.2% more of those with cancer of the corpus were past the menopause. The maximum incidence of cancer of the cervix is 10-25 yrs. following the birth of the last child; in the case of cancer of the corpus it is 15-30 yrs. Among married and widowed women with cancer of the cervix, there is a deficiency of childless women; among those with cancer of the corpus, the number of childless women exceeded the expected number. In the case of patients with cancer of the cervix and those with cancer of the corpus, no significant difference in survival rate was found between those who came under treatment within the 1st 6 mos. of noticing symptoms and those who delayed longer. The author emphasizes that this does not mean that there is no difference in survival between those in whom the disease is diagnosed and treated at an early stage and those who are in the later stages when they come under treatment. Treatment of cancer of the cervix in Stage I by Wertheim hysterectomy was most satisfactory; the results with radium alone were almost as good as those from operation and were not improved by courses of x-rays in addition. In Stage II, both the 5-yr. survival rate and the expectation of life were better after Ra treatment than after surgery, and in one small group, a preliminary course of x-rays, either before or after the radium treatment, gave improved 5-yr.-survival rate and actuarial expectation of life. In the case of cancer of the corpus, total hysterectomy with excision of the tubes and ovaries gave the best results in Stage I; results were not improved by the pre- or postoperative use of radiotherapy. The numbers of patients in Stages II and III who were treated were too small for the differences in 5-yr.-survival rates or expectation of life between different methods of treatment to be significant. There were 16 patients (1.9%) with cancer of the cervix who had undergone supravaginal hysterectomy, usually for the treatment of fibroids 1-18 yrs. previously. There were 3 nulliparae, one para-1, and the remainder, multiparae. [The article consists largely of tables in which much statistical information appears without interpretation.]—*Paul de R. Kolsch, M.D.*

Odell, Lester D., & Burt, James C. [Univ. Chicago Sch. Med., Ill.]: **New diagnostic adjunct for uterine cancer.** J. A. M. A. 142: 226-229; disc. 229-230, Jan. 28, 1950.—The method of determining β -glucuronidase activity is colorimetric. The test substance is phenolphthalein glucuronide, which is extracted from the urine of rabbits to which phenolphthalein diphosphate was administered. This substrate is incubated with the source of enzyme, the tissue, or the fluid to be tested, a process that liberates the phenolphthalein radical. If this solution is adjusted to an alkaline pH, a red color results. The intensity of the color is compared with known amounts of phenolphthalein, and the activity of β -glucuronidase is expressed as the μ g. of phenolphthalein liberated per gram or cubic centimeter of tissue or fluid per hour

of incubation. The data are arranged in 2 parts. The 1st concerns itself with the activity of this enzyme in vaginal fluid from women with and without cancer; the 2d lists the activity in histologically benign and cancerous tissues of the human female genitalia. Of the 2 methods, vaginal-fluid assay is easier and more practical for large surveys. Except for the cervix in pregnancy, a consistent difference in glucuronidase activity was observed between cases of histologically proved squamous-cell carcinoma (which were high) and histologically nonmalignant cervixes (which were low). Glucuronidase values for endometrial carcinoma, however, were within the range for nonmalignant endometrium. No correlation could be made between the type of benign pathological condition and the activity of β -glucuronidase in the tissue. Assays on the vaginal fluid can be read in 3 hrs. If increased activity (over 300 μ g.) is found, or if the vaginal fluid is contaminated with blood, any suspicious areas should be biopsied and assayed for tissue activity. Additional studies continue to reveal increased activity of β -glucuronidase in vaginal secretions and tissues of women with untreated cervical cancer. False positives occur in about 20% of cases. β -Glucuronidase is liberated by vaginal bacteria; the study of this phase of the problem continues.—*P. de R. Kolisch, M.D.*

Rich, Joseph; Angrist, Alfred A., & Carpenter, Frederick [Queens Gen. Hosp., Queens, N. Y.]: Gelfoam, vaginal smear, and biopsy in the diagnosis of uterine carcinoma. *Am. J. Obst. & Gynec.* 59: 1029-1033, May, 1950.—To test the Gelfoam biopsy method introduced by Gladstone, vaginal smears, Gelfoam biopsy, and formal biopsy were taken in 68 cases presenting signs and symptoms of possible uterine cancer.

No special instruments were used in the study. Smears were taken from the vaginal pool and by wiping across the suspected region, using initially a single cotton applicator and, later, the Gelfoam sponge proper to transfer the specimen to the glass slide. The sponge used was Gelfoam No. 12 (U-p-john) placed firmly against the cervix and then rubbed briskly across the surface. Because of poor staining, or of negative results when positive results were expected, approximately 10% of the smears were repeated and 7 Gelfoam specimens were recut.

There were 17 positive cases. Included was 1 case of carcinoma of the vulva, 1 of primary adenocarcinoma of the tube, and 2 of adenocarcinoma of the fundus. Except the 1 case of tubal adenocarcinoma that was sealed from the uterus, all of the Papanicolaou smears agreed with biopsy or surgical findings. In these same 16 cases, the Gelfoam results agreed in 13 instances, 2 remained falsely negative, and 1 suspicious. In the remaining cases, none of the Gelfoam preparations was falsely positive. 3 vaginal smears were falsely positive and 2 were classified as suspicious.

The Papanicolaou smear was found to permit meticulous cytological studies. The Gelfoam preparation gave less detail in nuclear structure but, except for the determination of invasiveness, corresponded to the ordinary tissue preparation to which

pathologists are accustomed. There was a definite timesaving feature in the Gelfoam studies, in that no specimen required more than 1 or 2 minutes for study. The Gelfoam sponge was found to be of ideal consistency to soak up and transfer material to slides, thus allowing smears prior to fixation and eliminating the use of applicators.

Both the smear and the Gelfoam biopsy were found to be worthy adjuncts in the diagnosis of carcinoma of the cervix, especially for surveys, and the Gelfoam procedure approached the accuracy of the vaginal smear, with the greater advantage of timesaving. Any visible lesion should be biopsied.—*A. A. Angrist, M.D.*

Wall, John A. [M. D. Anderson Hosp. Cancer Research, Methodist & Hermann Hosps., Houston, Tex.]. & **Klingensmith, William R., Jr.**: The effect of hysterectomy on carcinoma of the cervix. *Am. J. Obst. & Gynec.* 59: 901-905, Apr., 1950.—The cases in a representative group of rural and urban women divide into 3 categories: 1st, those in whom cancer was not recognized at the time of primary treatment; 2d, those who were subjected to inadequate treatment (simple total hysterectomy); 3d, those in whom an elective supracervical hysterectomy was done for a benign lesion and who later developed a "true carcinoma of the cervical stump." 62 (16%) developed cancer following hysterectomy; 23 (6%) developed "true carcinoma in the residual cervix." Nearly half of all patients who developed cancer following hysterectomy did so during the 1st 6 mos. following the operation, indicating that unrecognized cancer was present.

It is concluded that emphasis should be placed on the fact that where surgery is the procedure of choice, it must usually include a radical lymph-node dissection to be of value. The need for increased knowledge by the clinician of the growth behavior of tumors, and the fundamental principles of surgery and irradiation are emphasized.—*J. A. Wall, M.D.*

GENITOURINARY TRACT

Dodson, Austin Ingram: *Urological Surgery*. St. Louis. C. V. Mosby Co. 1950. 855 pp. \$13.50.—The 2d edition of this very valuable work continues to fill the gap left by the textbooks on urology. The common urological operations are clearly described and illustrated, while standard texts seldom more than name the procedures. In general, the steps described here are conservative and straightforward. Those not freely familiar with operative urology will find steady and reliable guidance in these pages, and the experienced operator can find worthwhile suggestions as well as a common-sense philosophy with which to temper his more fanciful surgical aspirations. Considerable advantageous revision of the 1st edition and a commendable attempt to bring the text up-to-date are evident. It is not possible to keep a book completely abreast of the times, so that the omission of a transthoracic approach to the kidney, and perhaps of a radical cystectomy with lymph-node dissection, is understandable. Radical groin dis-

section, however, is a reasonably standard procedure and, though briefly described incidental to more extensive procedures, would seem worthy of a detailed representation by itself.

In the 1st edition, the author states, "It was originally my intention to confine the book to surgical treatment, but . . . it seemed best to add some discussion of diagnosis and pathology . . ." Perhaps this plan is best, but such discussions are readily available in standard textbooks, and the omission of this material in a book primarily concerning operations proper would have permitted space for the inclusion of many worthy procedures. The author has rightly chosen to emphasize those techniques that his experience demonstrates are sound, yet interest might have been increased by telling of other methods, with a note of reserve added when indicated. Some readers will look for new though unestablished operations in such a book. Possibly a section on purely experimental techniques, so labeled, would elaborate the subject of urological surgery. However, these discussions, several by contributing authors, are particularly clear and authoritative even though they deal mostly with nonmanipulative aspects. Keyser's chapter on the endocrinology of prostatic carcinoma, Semans's on neurogenic bladder, Prather's on injuries, and Chapman's on acid-base balance are especially good. Certainly the purpose of a work influences its scope, and since this publication is partially directed at "surgeons lacking a basic training in urology," the additional feature of these discussions probably fits the program.

Among the minutiae that might be questioned are: the repeated suggestion of irrigating wounds with antiseptics; the statement that the most serious result of preoperative irradiation in cases of Wilms's tumor is leukemia; that the bladder should never be removed solely as a palliative measure.

All things considered, the book is a masterful contribution to urology and to surgery generally. The illustrations are plentiful and particularly clear and apt. The composition is easy to follow and well-worded. The publishers have contributed in no small measure to a deserved success. The book is trustworthy and praiseworthy and should be part of every well-rounded surgical library.—*V. F. Marshall, M.D.*

BLADDER

Jacobs, Arthur [Glasgow Roy. Cancer Hosp., Scotland]: *Carcinoma of the bladder. I. The treatment of cancer of the bladder by radium.* Brit. J. Radiol. 22: 393-398, July, 1949.—After a brief survey of the various methods of treatment of bladder tumors, the author describes a technique of interstitial irradiation that he has employed on selected cases. "The type most commonly selected for irradiation has been the solitary sessile broad-based papillary carcinoma, occupying the base and lower zones of the lateral walls. Infiltrative growths of the flat ulcerative or nodular type similarly located have been the other main varieties chosen." Through a suprapubic cystostomy, the bulk of the tumor is removed by electrocautery and/or elec-

trocoagulation, leaving a relatively small base into which 0.5 or 1.0 mg. radium needles are distributed according to the technique of Paterson and Parker. The aim is to attain a dose of 7000 r over a period of 160 hrs. in the tumor bearing area and in the zone 1 cm. peripheral to it. Except when dealing with small tumors, radium-element needles are preferred to radon seeds. Difficulties in obtaining an accurate distribution of the radium needles are mentioned. Early postoperative reactions to radium are described. The results of using radium on 110 selected cases of bladder cancer are given. There were 11 postoperative deaths, and 10 patients died of causes other than bladder cancer 2 to 5 yrs postoperatively. There were 52 deaths from bladder cancer within 5 yrs of operation. 37 patients survived 5 yrs. or more following treatment. Of the latter group, 1 died of bladder cancer in the 6th yr., 7 died of causes other than bladder cancer between the 7th and 15th yrs., and 29 were alive and clinically free from cancer for periods ranging from 6 to 11 yrs.—*W. F. Whitmore, Jr., M.D.*

Millen, J. L. E. [Christie Hosp. & Holt Radium Inst., Manchester, Eng]: *Carcinoma of the bladder. III. Treatment by radon seed implantation and deep x-ray therapy.* Brit. J. Radiol. 22: 402-405, July, 1949.—Experience with 2 radiotherapeutic methods of treatment of carcinoma of the bladder is reviewed. Radon seed implantation is the method of choice. Through a suprapubic cystostomy, the intravesical portion of the tumor is removed by diathermy. Radon seeds are then implanted in a single plane according to the Paterson-Parker rules, so that a margin of the tumor about 1.5 cm. wide is treated. After the implant has been completed, a urethral catheter is inserted and the suprapubic opening closed. An area 7 cm. in diameter is the maximum practicably treated by this technique. Multiplane and volume radon-seed implants are impracticable, precluding the effective treatment of tumors more than 1 cm. in thickness. Single and multiple growths can be treated by this technique. Radical deep x-ray therapy is, in general, employed in all bladder tumors that are beyond the limits of radon-seed implantation and yet not too advanced for hope of cure. A multifield, beam-directed technique is used, frequently using 6 fields arranged as a belt around the pelvis. Treatment is carried out with a 500 kv. x-ray unit delivering a tumor dose of 5500-6000 r in 5 wks. Radical treatment is contraindicated in the presence of distant metastases or when the primary tumor is too massive to be covered by an 8 x 10 cm. field. Of 280 patients, 31 were too advanced for treatment and 249 were treated by radiotherapy. 54 patients survived more than 5 yrs. Of 85 patients with noninfiltrating tumors, 60% of 55 patients treated with radon seeds alone and 23% of 30 patients treated with x-ray therapy alone survived 5 yrs. Of 83 patients with grossly infiltrating tumors, 15% of 39 patients treated by radon seeds alone and 7% of 44 patients treated by x-ray therapy alone survived 5 yrs. Palliative x-ray therapy was of little if any benefit except possibly in the control of hemorrhage.—*W. F. Whitmore, Jr., M.D.*

Riches, E. W. [Middlesex Hosp., London, Eng.]: **Carcinoma of the bladder. II. Some further aspects of treatment.** *Brit. J. Radiol.* 22: 398-402, July, 1949.—The influence of the type and site of a bladder tumor on treatment and prognosis is discussed briefly in general terms. The usefulness of combined treatment (cystodiathermy and x-ray therapy), cystodiathermy alone, x-ray therapy alone, and radium and radon therapy are pointed out. Partial cystectomy is considered the operation of choice for "accessible growths of moderate size, situated in the mobile part of the bladder." Of 46 patients having partial cystectomy, there were 7 (15.2%) operative deaths and 10 (21.7%) 5-yr. survivors. "Total cystectomy is indicated when papillary tumors are widespread, or when a nodular tumour is very large." Of 6 patients having one-stage bilateral intraperitoneal ureteroenterostomy, 2 (33.3%) died postoperatively. Of 39 patients having staged unilateral extraperitoneal ureteroenterostomy, 1 (2.5%) died postoperatively. Total cystectomy was done on 31 patients with 4 (12.9%) operative deaths. 7 patients were living for periods of from 2 mos. to 39 mos. postoperatively and 23 were dead within 2 yrs. of operation. Palliative ureteroenterostomy followed by x-ray therapy was employed in 14 cases that were considered incurable. In this group, there were 3 operative deaths and 4 patients alive for periods ranging from 6 mos. to 2 yrs.—*II*. F. Whitmore, Jr., M.D.

[Critical evaluation of the articles by Jacobs, Millen, and Riches, which comprise this symposium, is made impossible by the absence from all 3 presentations of any pathological grading of the tumors discussed. As a result, one can get only a hazy clinical impression of the type of tumor about which the particular author is writing; and different readers may well get different impressions. In Millen's series, the poor 5-yr.-survival rates for patients with grossly infiltrating tumors treated either by radon-seed implantation or by x-ray therapy offer some indication of the limitation of these techniques; these survival rates approximate those of patients with untreated vesical cancer!—*IV*. F. Whitmore, Jr., M.D.]

TESTIS

Roswit, Bernard; Sorrentino, J., & Yalow, Rosalyn [Veterans Admin. Hosp., Bronx, N. Y.]: **The use of radio-active phosphorus (P^{32}) in the diagnosis of testicular tumors: a preliminary report.** *J. Urol.* 63: 724-728, Apr., 1950.—A tracer dose of 300 to 500 μ c. of P^{32} was administered orally to patients with testicular enlargements. Readings were then taken with a Geiger-counter tube 2, 4, and 24 hrs. after the ingestion of P^{32} . The maximum counting rates were 300 to 600 counts per min. and were usually highest at the 24-hr. reading. The activity over the normal testicle was compared with the activity over the abnormal, enlarged testicle. The percentage differential counting rate was taken to be 100 times the difference between the counting rate of the normal and the abnormal testicles divided by the counting rate of the normal testicle.

A differential uptake of 25% was accepted as the upper limit for the normal testicle and for benign tumors. A difference of more than 25% was interpreted as suggestive of a malignant tumor. The figures (and their predictions) were compared with the final pathological diagnosis in 6 cases that came to surgery, and a correct preoperative diagnosis by the above described method was made in 1 case. In the 2 remaining cases, one false-positive and one false-negative reading had been obtained.—*H. E. E.*

HEMATOPOIETIC SYSTEM

Custer, R. Philip: **An Atlas of the Blood and Bone Marrow.** Philadelphia, W. B. Saunders Co. 1919. 321 pp. \$15.00.—The text of this Atlas is intelligently divided into categories, and is up-to-date in all of its concepts. There are excellent descriptions, in clear and concise form, of all of the major hematological disorders.

Many excellent photomicrographs in black and white have been presented, including both sections and smears of the bone marrow. It would be difficult to excel the majority of these reproductions. In addition, there are many Kodachrome photomicrographs that, in general, do not approach the excellence of those in black and white. In the reviewer's opinion, however, even these photomicrographs in color represent a real advance over the line drawings usually seen in atlases of this type. More realistic appearance is achieved, and although a certain fuzziness of outline is frequently present, the resulting total impression received is an accurate one.

Other atlases have defined cytological details more clearly, often at the expense of the general aspects of the subject of hematology. This Atlas can be criticized only in that it slightly de-emphasizes cytology. It concentrates on portraying the subject as an integrated system. It is, therefore, a useful addition to the available hematological atlases.—*T. R. Talbot, Jr., M.D.*

Peters, M. Vera [Toronto Gen. Hosp., Ont.]: **A study of survivals in Hodgkin's disease treated radiologically.** *Am. J. Roentgenol.* 63: 299-311, Mar., 1950.—The author gives a brief review of the classical historical contributions to the understanding and clarification of the present-day concepts of Hodgkin's disease. Many charts, graphs, and tables present sex incidence, sites of initial involvement, and nature of constitutional symptoms. Survival rates, both average and median, are elaborated. A clinical classification of the disease is discussed and its relationship to survival stressed, as is also that of age to response to radiation therapy. What makes this paper so germane is the report of an over-all 5-yr.-survival rate of 51% following radiation therapy.

It would seem well in critically assessing this paper to discuss the credits and debits of the author's findings and conclusions. It is the general belief of workers in this field, as is the author's contention, that progress of disease and ultimate survival in patients with Hodgkin's disease is

dependent upon the qualitative and quantitative presence and the gravity of constitutional symptoms, and the extent of disease involvement at the time the patient first appears for diagnosis and treatment. The sex male:female incidence of 2:1 agrees with most reports. Recent review of the clinical data in our own clinic seems to indicate that, whatever the reason, the survival is greater in women than in men. This too is in keeping with Dr. Peter's finding. The clinical classification of patients into Stage I, II, or III according to extent of involvement is a good one and bears out the significant correlation of survival to extent of disease involvement when the patient is first seen. It also emphasizes, *perhaps*, the greater importance of clinical criteria in prognosticating survival over that of the histological picture of Hodgkin's disease, i.e., granuloma, sarcoma, etc. Clinical classifications not unlike Dr. Peter's have appeared in the literature, and relationships to treatment and prognosis stressed.

To be noted and remarked upon critically are the following: 1. Most striking is the selection of cases. Of 257 patients treated, only 113 are reported as having the striking 51% 5-yr. survival. In addition (p. 308), a small group of acute cases are not included. This group would have a definite effect on survival statistics.

2. Hodgkin's disease in many instances is not a simple histological diagnosis to make, even for an expert pathologist, and one can only wonder about the following: (a) In the group of 113 cases, the pathologist includes 20 cases of "atypical" Hodgkin's disease. It is not stated definitely that further biopsy was actually obtained to prove the diagnosis. The so-called atypical Hodgkin's disease patients are stated as difficult to categorize until a further biopsy is obtained, from which one might infer that biopsy verification was obtained at a later date. (b) 20 patients were classified as *early* Hodgkin's disease by the pathologist and yet included in the group of 113 cases. Here also, there might be some disagreement. (c) Thus 40 of the 113 cases seem questionable as to histological interpretation.

3. The survival rate of 51% for 5 yrs. is essentially a reflection of the Stage-I cases, and partly of the Stage II, since 67% of the 113 patients were Stage I and Stage II. Most previous reports have given survival statistics without attempting a breakdown into classification.

4. The type, quantity, and kind of treatment (x-rays) given to Dr. Peter's patients do not appear to vary significantly from those that have been used rather extensively in many other clinics without achieving anything like her 5-yr.-survival figure of 51%. If it is considered that this high survival rate is due to prophylactic irradiation of the mediastinum and other clinically uninvolved sites (nodal areas), then it is difficult to comprehend how the small dosage of radiation given to these areas (400-800 r on 200 kv.) could materially influence the rate of progress and dissemination of Hodgkin's disease. It must always be remembered that the natural history of Hodgkin's disease varies considerably in different patients, and even, at

times, in the same patient. Though the author does not consider the 17% improvement in 5-yr.-survival rate in the cases irradiated prophylactically as significant, it would seem necessary to compare only Stage-I patients to determine this point. This, unfortunately, she does not do.

5. The total number of pathologically proved cases from which the statistics are concluded is small: 113 for 5-yr. survivals, and 54 for 10-yr. survivals.

6. It is questionable that if a recurrence resists irradiation of one quality it may respond to another quality "since the response to therapy varies considerably."

7. The higher survival rate among women should spur on interested clinicians to further their study of endocrinological factors in Hodgkin's disease.—H. D. Diamond, M.D.

Riley, W. Champ, & Gaillard, Louis [Hop. Cantonal, Geneva, Switz.]: **Significance of anemia, leukopenia and Pel-Ebstein fever in Hodgkin's disease.** Arch. Int. Med. 85: 795-803, May, 1950 — This is a review article on the triad of anemia, leukopenia, and Pel-Ebstein fever associated with Hodgkin's disease, noting 15 cases collected from the literature to which the authors add a case of their own. The relation of this triad to the presence of occult abdominal Hodgkin's disease is correctly stressed.—H. D. Diamond, M.D.

MUSCULOCUTANEOUS SYSTEM

Heller, Elwyn L., & Sieber, William K. [Univ. Pittsburgh Sch. Med., Pa.]: **Fibrosarcoma; a clinical and pathological study of sixty cases.** Surgery 27: 539-545, Apr., 1950.—The clinical and pathological features of fibrosarcoma are reviewed in 23 men and 37 women patients, more than 66% in the age span of 40-69 yrs. Potential etiological relationships appeared in 9 cases: 2 had multiple neurofibromatosis; 1 arose in a varicose ulcer, 1 in a mastectomy scar, 1 in a lesion of osteitis fibrosa cystica, 3 in longstanding, pre-existing tumor masses, and 1 followed severe trauma by 4 mos. The primary lesion was retroperitoneal or visceral in 22 instances. The head and neck was involved in 10 instances, extremities in 15, trunk in 11, and 2 cases were unspecified. The course was unpredictable, and of 21 patients subjected to surgical excision, 11 developed recurrences within a yr. Long-term survivals were those treated by surgery or surgery plus x-rays, although 1 patient lived more than 6 yrs. after x-rays and died of fibrosarcoma. Death is usually due to distant metastases. In 7 autopsied cases, lung metastases were noted in 4 and regional-node involvement in 3. Blood-borne metastases are the rule. Prognosis could not be correlated accurately with histological grading, with site of origin, nor with duration of the tumor prior to therapy. Recurrence after excision was a poor prognostic sign. Of the 60 patients, 37 were followed to death (1 lived 6 yrs.), 11 were lost, and of 12 living, there were 3 surviving past 3 yrs. and 2 past 5 yrs.—R. C. Hickey, M.D.

SKIN

Cowdry, Edmund V. [Washington Univ. Sch. Med., St. Louis, Mo.]. & Andrew, Warren: Some cytochemical and cytologic features of senile keratosis. *J. Gerontol.* 5: 97-111, Apr., 1950.—Biopsies of clinically benign senile keratoses from the head and neck regions of 8 patients, ranging from 40 to 81 yrs. of age, were studied by routine staining, demonstration of elastic tissue, cytochemical studies for ribonucleic acid, and microincineration. Hypertrophy of the epidermis with many papilliform downgrowths was often accompanied by areas of epidermal atrophy. Parakeratosis was frequently evident in the less hypertrophic and in the atrophic areas. In parakeratotic regions, the stratum corneum retained its nuclei and a stratum granulosum was generally lacking. The cellular features included discrepancies in cell size, perinuclear vacuolization, hypertrophy of the nucleolus, tendency to internal division of the nucleus with vesicle formation, and amitotic nuclear division. Mitoses were not very common and no pathological mitoses were seen. The distribution of mineral ash varied in abundance with the histological features. In general, it was less abundant than in normal epidermis. No marked changes in amount of ribonucleic acid were noted. Frequently, lymphocytes accumulated in the underlying dermis, in which there was also degeneration of elastic tissue.—A. G. Foraker, M.D.

Lennox, Bernard [Postgrad. M. Sch. London, Eng.]: Pigment patterns in epithelial tumours of the skin. *J. Pathl. & Bact.* 61: 587-598, Oct., 1949.—Three hundred and eleven biopsies from 226 patients (some from multiple tumors and others serial biopsies during radiotherapy) were studied, with emphasis on the silver technique of Masson for the demonstration of melanin: (1) squamous papilloma—51 cases, of which 34 (67%) contained melanin; (2) benign calcifying epithelioma—3 cases, all nonpigmented; (3) squamous carcinoma—51 cases, none pigmented; (4) rodent ulcer and related tumors—124 cases, of which 16 (37%) contained melanin.

Melanoblasts were demonstrable in pigmented tumors in nearly all cases. Production of melanin by the epithelial cells of these tumors is considered improbable. In pigmented tumors, the pigmentation may assume any of 3 patterns: (1) a small number of squamous papillomas retain the structure and type of pigmentation of normal skin; (2) most squamous papillomas show melanoblasts along the basement membranes and little melanin in the epithelial cells; (3) rodent ulcers and squamous papillomas of the verruca-senilis type have their melanoblasts scattered through the cell groups and their epithelial cells are uniformly and heavily pigmented.

The mere presence or absence of visible melanin is of little value in the classification of epidermal tumors. These studies show that the presence of the readily visible melanin which leads to the labeling of an epithelial tumor as "pigmented" is merely an exaggeration of an extremely common process.—A. G. Foraker, M.D.

NERVOUS SYSTEM

Globus, Joseph H. [Mt. Sinai Hosp., New York City]: Brain tumor, its morphology in relation to prognosis. *J. Mt. Sinai Hosp.* 16: 335-378, Mar./Apr., 1950.—All physicians, general pathologists in particular, will be warmly disposed toward Dr. Globus, since he presents a simple, workable classification of brain tumors without resorting to the usual dissertation on special staining techniques or the controversial subject of nomenclature. The paper is concerned primarily with the presentation of criteria that would enable one to predict the behavior of a given tumor and to select those in which a forecast of a favorable surgical outcome can be made.

The author resolves the histological types of glioma into the 2 simple categories of spongioblastoma and transitional glioma and justifies this classification by a presentation of the comparative clinical behavior of approximately 200 documented cases. 2 statements are made that deserve wide dissemination, namely, that there is probably no such tumor as benign glioma, and that it is the most cancerous or undifferentiated focus of cells, no matter how small, that regulates the cancerous growth potential of a tumor. Those that argue against the existence of a neuroblast component of meningeoepithelial tumors will find little solace in the splendid microphotographs of giant-cell neuroblasts included by the author. The surgically unpromising aspect of this group of neoplasms is reflected in the paucity of cures following operation (none in the author's series).

The medulloblastoma is considered a universally fatal tumor because of its undifferentiation, rapid growth, precarious location, and tendency to spread along the subarachnoid space.

The ependymoma is mostly infiltrating and inaccessible, therefore unpromising. There are a few recorded cases of circumscribed tumors of the 4th ventricle that have been successfully removed.

The autochthonous brain tumors (craniopharyngioma, pinealoma, and infundibuloma), because of their inaccessibility and the hazards of compromising important structures, are not amenable to surgery of the type that would afford a lasting cure. A few of the cystic variety can be drained for temporary relief. The success claimed by the radiotherapist in treating the pinealoma has no substantial proof.

Regarding pituitary tumors, it is the consensus, at present, to use irradiation when they are recognized early and surgery when vision is dangerously threatened.

Metastatic tumors comprise almost 10% of all brain tumors. The anatomical behavior of this group precludes any worthwhile extension of survival period by surgical intervention. Surgical restraint and close liaison among neurosurgeon, internist, and neurologist are more and more insuring against avoidable errors in the handling of this type of case.

In the opinion of this reviewer, this presentation could be profitably read by all physicians engaged in the practice of medicine.—E. F. Murray, M.D.

Hoefel, Paul F. A., & Cohen, Sidney M. [Columbia Univ., Coll. Phys. & Surgeons, & Neurol. Inst., New York City]: **Localization of cord tumors by electromyography.** *J. Neurosurg.* 7: 219-226, May, 1950.—Normal resting striated muscle in man shows no action potentials. In response to irritative stimulation of the lower motor neurone anywhere from the anterior horn cell down, motor unit action potentials, electrical equivalents of fascicular twitches, may be recorded. Clinical or subclinical wasting of muscles is also accompanied by motor unit discharges. Systematic exploration with coaxial needle electrodes of skeletal muscles according to their segmental supply can thus be used as a test for the determination of the level of lesions of the spinal cord.

This presentation is based on 88 cases with a total of 91 cord lesions verified by operation, autopsy, or unequivocal x-ray findings. 83 of the lesions occurred at well-defined levels. In the other 8, widespread or multiple lesions, as syringomyelia or multiple melanomas, were found. 69 of the 83 lesions (83.1%) and all 8 diffuse lesions were properly localized and outlined. In 5 instances (6.1%) of lesions with well-defined level, widespread electromyographic activity (including the correct level) was recorded but was unsuitable for localization. In 6 instances (7.2%), no electrical activity was found; in 3 (3.6%), false levels were found. The electromyographic findings were verified in 77 of the 91 lesions (84.6%).—*P. F. A. Hoefel, M.D.*

Netsky, Martin G.; August, Burton, & Fowler, William [Montefiore Hosp., New York City]: **The longevity of patients with glioblastoma multiforme.** *J. Neurosurg.* 7: 261-269, May, 1950.—In a series of 70 cases of glioblastoma multiforme, a greater proportion of men than women was found, with the ratio 1.8:1. 5 patients survived 6 yrs. or longer from the time of the 1st symptom, the longest being 14 yrs. The latter is the longest survival period on record in a verified case of glioblastoma multiforme. An analysis of factors in survival revealed that operation had no significant effect on longevity; irradiation a slight effect, if any. The longest survivals occurred in patients with onset at 24 to 42 yrs. of age. However, age at onset was not a constant prognostic factor. The sex of the patient, the location of the tumor, or the histological appearance gave no indication as to longevity. A significant lengthening of survival was found in those patients whose initial symptom was a focal motor seizure. While this was generally true, some patients with this symptom had a short survival. At the present time, there is no means, clinical or histological, of predicting whether or not a given patient will survive longer than the average. The possibility is considered that, in certain cases, an originally benign tumor becomes malignant and is seen as a glioblastoma multiforme at autopsy. It is suggested that in reporting survival in tumors of the nervous system, the survival from the first symptom as well as the postoperative survival be given.—*M. G. Netsky, M.D.*

Toumey, James W.; Poppen, James L., & Hurley, Melvin T. [Lahey Clin., Boston, Mass.]:

Cauda equina tumors as a cause of the low-back syndrome. *J. Bone & Joint Surg.* 32-A: 249-256, Apr., 1950.—In the 10-yr. period from January, 1939, through December, 1948, 48 patients with tumors of the cauda equina were operated upon at the Lahey Clinic. It is often difficult clinically to differentiate cauda-equina lesions from disc lesions, which they may simulate closely. The most common single physical sign characteristic of cauda-equina tumor is absence or impairment of the knee jerks. Complete subarachnoid block was present in 19 cases. The most important diagnostic factor is the myelogram (pantopaque preferred). Estimation of the total protein of the cerebrospinal fluid is also of value; a level of more than 100 mg. suggests a diagnosis of tumor.

In one fifth of the cases, the tumors were malignant. Neurilemoma is the most frequent benign tumor.—*H. E. E*

Wittenborg, Martin H. [Children's M. Center, & Harvard M. Sch., Boston, Mass.]: **Roentgen therapy in neuroblastoma; a review of seventy-three cases.** *Radiology* 54: 679-688, May, 1950.—These 78 cases all with complete microscopic confirmation included twenty-eight that received no therapy and 45 treated by surgery, surgery and postoperative x-ray therapy, or x-ray therapy only. Patients in whom the neuroblastoma was primary in, or showed extensive involvement of, the central nervous system and patients who have received either radioactive drugs or nitrogen mustard, or antifolic acid derivatives were not used since it was hoped to evaluate the x-ray effects without the introduction of such additional factors.

Of the reported series, 30% survived 3 or more yrs., some having been followed up to 16 yrs.

As in most cases of malignant growth, early detection and complete surgical excision of the local tumor appeared to offer the best prognosis: approximately 60% 3-yr. survival in the reported series.

If surgical excision of the primary tumor was incomplete and no metastases were present, postoperative irradiation appeared to offer a good prognosis, with approximately 60% 3-yr. survival.

The site of the primary lesion appeared to be of less importance than the presence and distribution of metastases. With skeletal metastases, death uniformly occurred within a yr., irrespective of surgical or x-ray therapy. Involvement of both chest and abdomen, whether by direct extension or lymphatic spread, proved fatal in all patients. Primary neuroblastoma in the abdomen with metastases limited to the liver, however, offered an excellent prognosis if treated by irradiation. A 100 per cent 3-yr. survival in this group of 6 patients was reported.

The technique of irradiation is presented in detail. In the group of patients who survived without complications of treatments, the initial tumor doses ranged from 800 to 1200 r in 10 to 14 days, usually followed by a second comparable series in 3 mos. Deep x-ray therapy was given in fractionated daily doses of approximately 200 r in air daily at 200 kv. with 0.5 mm. Cu and 1 mm. Al filtration, the beam having a half-value layer of 1.55 mm. of

Cu. The feat that large initial doses may initiate fatal hemorrhage was not proved to be well founded. All radiation was given postoperatively as soon after surgery as possible without waiting for healing of the surgical incision. The initial therapy was usually given through a port opposite the surgical excision, which fell in the exit port. The limiting dosage factor was found to be the volume of hematopoietic tissue exposed to irradiation, not the skin. In this series, a single fatality as a result of x-ray therapy was observed.—*M. H. Wittenborg, M.D.*

OSSEOUS SYSTEM

Coley, Bradley L., & Harrold, Charles C., Jr. [Memorial Hosp., New York City]: An analysis of fifty-nine cases of osteogenic sarcoma with survival for five years or more. *J. Bone & Joint Surg.* 32-A: 307-310, Apr., 1950.—This study was undertaken in an effort to explain why some patients survive 5 yrs. or more, while the majority of patients with osteogenic sarcoma succumb to the disease. 59 5-yr. survivals of osteogenic sarcoma, from a group of 252 determinate cases treated during the period from 1917 through 1943, form the basis of the present survey. About two thirds of the cases were fibrosarcoma or chondrosarcoma; these tumors tend to metastasize later than "osteogenic sarcoma." The greatest number of 5-yr. survivors were treated surgically, mostly by amputation rather than by conservative surgery. The authors have abandoned the routine use of the toxin treatment for osteogenic sarcoma. There were no 5-yr. survivals in the present series of those in whom the lesion was located in the proximal end of the femur. 1 patient is living and well 3 yrs. after lobectomy for pulmonary metastasis and 8 yrs. after amputation for the primary growth.—*H. E. E.*

Prevo, Samuel Bradley [Campbell Clin., Memphis, Tenn.]: A clinical analysis of 205 cases of malignant bone tumor. *J. Bone & Joint Surg.* 32-A: 298-306, Apr., 1950.—A clinical analysis is made of 205 cases of malignant bone tumor, all histologically proved. Cases with inadequate follow-up were not included in the study; neither were any of the non-neoplastic diseases such as Paget's disease, scurvy, rickets, osteitis fibrosa cystica, and dental tumors. At the Campbell Clinic, 702 patients with bone tumor have been encountered, and of these cases, 287 were considered benign. The commonest type of malignant tumor in this series is Ewing's tumor and the least common, multiple myeloma. The results in malignant bone tumors are almost invariably bad. Favorable results after 5 yrs. in cases of Ewing's tumor do not assure freedom from metastasis; in other types of malignant bone tumors they are more indicative of a permanent cure. The most logical treatment is early amputation followed by irradiation. [Many observers do not subscribe to postoperative radiation therapy following amputation for malignant bone tumors.]—*H. E. E.*

Upshaw, Jackson E.; McDonald, John R., & Ghormley, Ralph K. [Mayo Clin., Rochester,

Minn.]: Extension of primary neoplasms of bone to bone marrow. *Surg., Gynec. & Obst.* 89: 701-711, Dec., 1919.—The authors have undertaken a study of the characteristics of extension to bone marrow displayed by 50 osteogenic sarcomas, 20 Ewing sarcomas, and 5 chondrosarcomas. All were in the long bones of extremities, which had been amputated before death. Sections of the marrow were taken for microscopic study at short intervals proximal and distal to the gross medullary involvement of each tumor. The limits of medullary involvement depicted on preoperative x-rays were measured and compared to the gross and microscopic extent. There was an attempt to correlate neoplastic medullary extension with survival rate in the types studied.

In no case could a defect in the continuity of the medullary neoplastic progression away from the principal lesion be definitely established. Thus grave doubts were cast upon the existence of primary tumor emboli in the same bone.

Medullary extension from a primary bone sarcoma may and frequently does occur without x-ray evidence of its presence. In this series, microscopic extension exceeded x-ray extension in 31% of osteogenic and 36% of Ewing sarcomas. Neoplastic medullary involvement may be found microscopically for a considerable distance beyond any gross evidence. 3 cases of osteogenic sarcoma exhibited microscopic extension to the line of amputation. These facts indicate the fallacy of relying upon visual inspection for extent of bone involvement.

Ewing's tumor exhibited the greatest, osteogenic sarcoma the next, and primary chondrosarcoma the least, tendency to spread in bone marrow.

From the statistics presented, it would appear that in osteogenic sarcoma better results had been obtained by radical amputation above the bone containing the lesion.—*E. F. Murray, M.D.*

RESPIRATORY TRACT

Rawson, Arnold J.; Eyler, Paul W., & Horn, Robert C., Jr. [Hosp. Univ. Pennsylvania, Philadelphia]: Plasma cell tumors of the upper respiratory tract; a clinico-pathologic study with emphasis on criteria for histologic diagnosis. *Am. J. Path.* 26: 115-161, May, 1950.—The clinical and histological features of 9 cases of plasma-cell tumor involving the upper-respiratory and food passages were reviewed. Criteria for the separation of those extramedullary plasma-cell tumors that might be expected to behave as malignant neoplasm were searched for since the usual cytological characteristics of malignancy are often absent. This study suggested the most important features of malignancy are (1) the presence of broad sheets of cells oriented on a delicate vascular stroma and (2) replacement of tissue by tumor cells rather than infiltration of tissue.

Of the 9 cases of tumors of the upper respiratory passage, 6 were considered malignant; all involved multiple areas. Of these 6 cases, 1 was associated with widespread bone and soft-tissue involvement,

another showed generalized, and 1 regional, lymph-node involvement. In 2 cases, bone was involved in the locally destructive process. In contrast the clinically benign plasma-cell lesions were small, well localized, and noninvasive.

Radiation therapy is considered the treatment of choice in the malignant plasma-cell tumors. Recurrence was the rule in cases treated by surgical removal.—*K. P. Knudtson, M.D.*

SINUSES AND LARYNX

Baclesse, F. [Fond. Curie, Paris, France]: **Carcinoma of the larynx. Radiotherapy of laryngeal cancer; clinical, radiological and therapeutic study; follow-up of 341 cases treated at the Fondation Curie, from 1919 to 1940.** *Brit. J. Radiol. suppl.* 3, pp. 1-62, 1949.—During the period from 1919 to 1940, 341 patients with laryngeal cancer were treated with radiation. Cancer of the larynx is defined anatomically and radiologically. [The author does not include tumors of the peripheral portions of the extrinsic larynx and of the postcricoid region but classifies such types as belonging to the hypopharynx. If such lesions are excluded from a clinical survey of laryngeal cancers, the end results appear more favorable, since postcricoid tumors and lesions of the peripheral portions of the extrinsic larynx are more malignant, metastasize to the cervical lymph nodes more frequently, and do not respond to treatment as well as growths of the intrinsic larynx.] On the basis of x-ray studies, the cases are further classified into supraglottic, glottic, and subglottic growths. [The evidence offered in support of an x-ray classification for laryngeal cancer is inadequate and unconvincing.]

X-ray therapy was used as a sole method of treatment in 234 cases and a 5-yr.-cure rate of 20% was obtained. In 55 cases in which recurrences occurred after initial treatment by surgery (partial or total laryngectomy), a 5-yr.-cure rate of 18% was obtained. In those cases treated by radiation in which cervical metastasis was present, the 5-yr.-cure rate was 4%, and up until the year 1940, no such patient had ever survived 5 yrs. The technique employed at the Curie Institute is described in detail.—*H. E. E.*

Fitz-Hugh, G. S. [Sch. Med., Univ. Virginia, Charlottesville]; Moon, C. N., Jr., & Lupton, C. H., Jr.: **Cytological smear technique in the diagnosis of carcinoma of the maxillary sinus: preliminary report.** *Laryngoscope* 60: 376-387, Apr., 1950.—Antial washings in 72 suspicious cases were examined, using the Papanicolaou technique. In 6 cases, the smear was indicative of cancer, and in all of these, the diagnosis was subsequently confirmed by formal antial biopsy. No false positives or false negatives were found in any of the 72 cases.—*H. E. E.*

Gunderson, R. W. [Middlesex Hosp., London, Eng.]: **Appendix: A report on 216 cases of cancer of the larynx treated with X rays only at the Fondation Curie, Paris.** *Brit. J. Radiol. suppl.* 3, pp. 63-68, 1949.—The survey covers a

period from 1919 to 1940. All cases were determinate. The prognosis is better in those cases in which fibrinous reaction (due to radiation therapy) is avoided. The incidence of laryngeal necrosis is less when a fibrinous reaction is not obtained. [The latter portion of this report is largely a mathematical analysis of the Curie Institute cases, although no significant conclusions are reached.]—*H. E. E.*

BRONCHI

Bogardus, George M. [Kalispell, Mont.]; Adams, William E., & Phillips, Francis J.: **Bronchiogenic carcinoma. II. The correlation of pathologic characteristics and clinical manifestations in unresectable and unexplored post-mortem lung tumors.** *J. Thoracic Surg.* 19: 699-708, May, 1950.—A study was made of carcinoma of the lung that was explored but found to be nonresectable and carcinoma of the lung not operated upon but discovered at autopsy. Of the operated, but nonresected, carcinomas of the lung, 16 were undifferentiated; 14 were squamous-cell tumors without pearl formation; 4 were mixed forms containing more than 1 cell type; and 2 were adenocarcinomas. The mixed forms of tumor are worthy of comment in that they demonstrate that, for a really reliable diagnosis and study, large microscopic sections are indispensable, as has been emphasized by Phillips and co-workers.

36 autopsied carcinomas were studied: 15 of these were adenocarcinomas; 14 were undifferentiated tumors; 6 were squamous-cell tumors; and 1 was a combination of adenocarcinoma and nonkeratinizing-cell tumor. In this small series, the adenocarcinomas and the undifferentiated or oat-cell tumors tended to lie towards the periphery and spread not only to mediastinal structures but, also, to distant organs via the blood stream. The squamous variety tended to occupy a somewhat more central location and spread chiefly through the adjacent mediastinal structures.

It is felt that, in lung carcinoma, there is some correlation as to cell type and clinical course of the disease. The tumors that appear to be less amenable to surgical therapy are largely the poorly differentiated and the adenocarcinomas. This impression is derived from the fact that the autopsied, and the explored but not resected, tumors were composed of 30 undifferentiated tumors; 17 adenocarcinomas; 16 nonkeratinizing squamous tumors; and but 4 keratinizing squamous-cell tumors and 5 mixed forms containing more than 1 cell type. In contrast to this, Phillips and associates found that all of their resected tumors were squamous-cell in part or in entirety.—*G. M. Bogardus, M.D.*

Phillips, Francis J.; Basinger, Clair E., & Adams, William E. [Univ. Chicago Sch. Med., Ill.]: **Bronchiogenic carcinoma. I. A pathologic clinical correlative study of full-size mounts from operated carcinomas.** *J. Thoracic Surg.* 19: 680-698, May, 1950.—The controversy among clinicians and pathologists regarding the pathogenesis of primary carcinoma of the lung stimulated us to

make and study full-sized mounts of representative cross-sections of all tumors of the lung removed. An attempt was made to correlate the type of tumor, the site of the tumor, and the size of the tumor with the clinical manifestations as demonstrated by history, physical, radiological, and bronchoscopic examination, and by findings at exploration. The cell type has been studied in its relationship to the site and size of the tumor, the rate of growth, the extension into contiguous tissues, and metastases to other organs. Of the 40 cases thus studied, 27 were found to be of squamous-cell type with or without pearl formation and 13 exhibited both epidermoid and adenocarcinoma.

A similar study was made of 36 nonresectable tumors and 36 unexplored cases in which tumors were found at autopsy. Of the nonresectable group, approximately half were of an undifferentiated cell type. The others were of a nonkeratinizing squamous-cell variety. Of the tumors studied from autopsy specimens, 15 were adenocarcinoma, 14 were undifferentiated-cell, 6 were epidermoid, and 1 a mixture of adeno- and squamous-cell carcinoma. Illustrations of these factors are presented and their significance discussed.—*F. J. Phillips, M.D.*

Van Hazel, Willard; Holinger, Paul H., & Jensik, Robert J. [Univ. Illinois Research & Educational, & St. Luke's Hosps., Chicago, Ill.]: Adenoma and cylindroma of the bronchus. *Dis. of Chest* 16: 146-166; disc. 166-168, Aug., 1949.—The authors present a series of 20 cases of bronchial adenoma and 2 of cylindroma, and analyze it according to history and to clinical, x-ray, and bronchoscopic findings. The gross and microscopic pathology is discussed in order to emphasize the difference between adenomas. The adenomas are considered to be extremely slow-growing but invasive tumors, whereas cylindromas [in some laboratories called adenoid cystic carcinoma] meet all the criteria of malignant lesions.

10 of the adenomas were treated by bronchoscopy alone; 5 were completely removed and the patients are symptom-free; 4 partially removed, 1 only biopsied. 10 were treated surgically: 7 by pneumonectomy, of whom 4 are living and well, 2 improved, 1 died postoperatively; 3 by lobectomy, of whom 1 each is living and well, improved, and dead.

Of the 2 cases of cylindroma, 1 was treated bronchoscopically for 5½ yrs. merely in an attempt to maintain an airway (the tumor had invaded the trachea at the time of diagnosis). At autopsy, metastases were found in hilar lymph nodes, the other lung, and kidney. The other patient was treated by immediate pneumonectomy but had a recurrence 5½ yrs. later.—*D. A. S.*

LUNG AND PLEURA

Campbell, William N. [Temple Univ. M. Sch., Philadelphia, Pa.]: Pleural mesothelioma. *Am. J. Path.* 26: 473-487, May, 1950.—A review of 4 autopsied cases of pleural mesothelioma occurring in 3533 consecutive autopsies at Temple University Hospital is given. The criteria used for selecting

cases of pleural mesothelioma were: a gross picture of a firm pleural mass encasing the involved lung, the lack of a demonstrable primary tumor in the lung or elsewhere in the body, and a histological picture compatible with that previously described in the literature.

It is stressed that pleural mesotheliomas usually demonstrate a histological structure that appears epithelial in some areas and mesenchymal in others. This feature has been previously emphasized by many authors. Occasionally, cases are reported that show only the epithelial component.

The characteristic method of spread is by contiguity and serosal seeding. Regional lymphatic metastasis and occasional vascular spread may occur, although these are uncommon. In cases 1 and 2, the tumor diffusely infiltrated the lung. [From the microscopic description and photomicrographs, the question arises whether these tumors are not terminal bronchiolar carcinoma arising within pulmonary parenchyma and secondarily invading the pleura. It would seem more probable that this sequence of events occurred, in view of the distinct alveolar pattern. Although stains for mucin are not reported, they would be of distinct interest in that mucin is frequently found intra- and extracellularly in terminal bronchiolar carcinoma.]—*K. P. Knudtson, M.D.*

Farber, Seymour M.; Rosenthal, Milton; Alston, Edwin F.; Benioff, Mortimer A., & McGrath, Allen K., Jr.: *Cytologic Diagnosis of Lung Cancer*. Springfield, Ill. Charles C Thomas, 1950. 80 pp. \$6.00.—This book is the first original monograph solely devoted to the cytological diagnosis of lung cancer. The monograph is divided into 11 chapters and illustrated by 10 color plates.

The most recent statistical data on the increasing incidence of pulmonary cancer and its present status of therapy are presented in a clear and comprehensive manner. The many failures in the cure of lung cancer are attributed by the authors to late and inadequate diagnostic methods. The cytological evaluation of pulmonary exudates is therefore recommended as a routine, simple procedure for morphological diagnosis of cases with minimal thoracic symptoms and for differential diagnosis of lung cancer simulating other diseases.

A detailed review of the literature on the cytological diagnosis of lung neoplasms is given from the sporadic attempts of the last century up to its present widespread use. The Papanicolaou method for fixation and staining of wet smears is praised as the most satisfactory. However, the use of alcohol as a fixative in the collection of sputum and glycerin for preservation of fixed, unstained smears is not recommended by the authors. It must be pointed out that, owing to dryness, the loss of nuclear details and cellular hypertrophy are often evident in nonfixed and inadequately preserved specimens.

The histology of the normal respiratory tract and the histology of benign and malignant pulmonary neoplasms are presented clearly and concisely. The incidence of the various malignant pulmonary neoplasms is described according to the cell type, age,

but the activity of these enzymes increased markedly in the carcinoma. The level of cytochrome c likewise remained unchanged in precancerous epidermis, but decreased in the carcinoma. On the other hand, cytochrome-oxidase activity in late hyperplastic epidermis was twice that of normal epidermis, but its activity decreased in the carcinoma. Of the many constituents studied in hyperplastic epidermis, cytochrome oxidase is the only component that has changed significantly prior to cancer.

The distribution of 12 amino acids in the carcinoma was quite similar to that of the precancerous epidermis and, therefore, showed no distinct pattern characteristically different from noncancerous tissue. With paper chromatography, hyperplastic epidermis was found to contain larger amounts of free amino acids than normal epidermis, while the carcinoma showed an over-all decrease in these compounds. With the same technique, a consistent pattern of free amino acid distribution was found in squamous-cell carcinomas and in some other cancer tissues, while most normal tissues differed from each other in this respect.

These studies on the epidermis of mice undergoing carcinogenesis have demonstrated that the assessment of chemical changes due to alterations in cell types from those characteristic of real precancer are difficult to evaluate. Until methods become available for localizing the precancerous foci in epidermis or in any other tissue, a study of the chemistry of the intermediate stages in carcinogenesis is practically impossible.—*C. Carruthers, Ph.D.*

Koletsky, Simon; Bonte, Frederick J. & Friedell, Hymer L. [Western Reserve Univ. Sch. Med., Cleveland, Ohio]: **Production of malignant tumors in rats with radioactive phosphorus.** *Cancer Research* 10: 129-138, March, 1950.—The development of malignant neoplasms was one of the late effects observed in rats injected with large doses of P^{32} . 13 tumors were studied, of which 10 were osteogenic sarcomas situated most frequently in the jaw and also occurring in the spine, tibia, femur, or ilium 4 metastasized to the lung. There were 3 squamous-cell carcinomas involving the face and associated with exophthalmus. The incidence of tumor development was about 40%.

The neoplasms occurred in animals which received (1) a single LD_{50} dose of P^{32} , 4.5 μ c./gm. body weight (average latent period of 290 days) and (2) repeated doses of 1.5 μ c./gm. P^{32} (average latent period of 165 days).

P^{32} is deposited heavily in the skeleton and produces radiation damage to bone. The changes have been described under the term "radiation osteitis" and consist essentially of degeneration and necrosis of old bone accompanied by reactive formation of new bone that is usually atypical in arrangement and staining and often fibrous. Frequently the new bone also becomes devitalized. In these studies such bone changes, although varying in degree, were observed almost constantly. There is strongly presumptive evidence that the lesions serve as a precursor to malignancy although the precise steps in the metamorphosis are not known.

If this concept is correct, the neoplasms occur as part of, or as the end result of, atypical bone growth representing attempted regeneration in regions of radiation necrosis.—*S. Koletsky, M.D.*

Law, L. W. [Nat. Cancer Inst., Bethesda, Md.]: **Studies on the effects of a guanine analog on acute lymphoid leukemias of mice.** *Cancer Research* 10: 186-190, March, 1950.—A definite, regular, and reproducible inhibition of 2 transplantable acute lymphoid leukemias in mice resulted from parenteral administration of the guanine analog, 8-azaguanine (guanazolo) at dosage levels of 25 to 112.5 μ g./gm. body weight.

No specific inhibition was observed on a transplantable lymphosarcoma.

Apparent release of inhibition by use of guanine HCl was observed.—*L. W. Law, Ph.D.*

Mühlbock, O. [Lab. Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Amsterdam]: **Mammary tumor-agent in the sperm of high-cancer-strain male mice.** *J. Nat. Cancer Inst.* 10: 861-864, Feb., 1950.—It is conceivable that in mice the mammary tumor agent is transmitted from high-cancer-strain males to low-cancer-strain females and is responsible for the higher tumor rates in the hybrids. One possibility is that the agent is transmitted by the sperm. Therefore the sperm of high-cancer-strain dba males was tested for the presence of the mammary tumor agent. The injection of sperm from the cauda epididymidis into sensitive hybrids gives rise to a high percentage of mammary tumors. Comparison of the tumor percentages in animals treated with sperm and with the milk factor and with blood reveals that the concentration of the agent in the sperm is certainly not minimal. The finding of the mammary tumor agent in the sperm makes it highly probable that transmission of the agent may take place in copulation.—*O. Mühlbock, M.D., Ph.D.*

Sugiura, Kanematsu [Sloan-Kettering Inst., New York City]; **Hitchings, George H.; Cavalieri, Liebe F., & Stock, C. Chester:** **The effect of 8-azaguanine on the growth of carcinoma, sarcoma, osteogenic sarcoma, lymphosarcoma and melanoma in animals.** *Cancer Research* 10: 178-185, Mar., 1950.—This paper deals with a study of the influence of 5-amino-7-hydroxy-1*H*-*v* triazolo [d] pyrimidine, or so-called 8-azaguanine, upon the growth of several well-known transplantable tumors in animals. Repeated intraperitoneal injections of 8-azaguanine at all levels, 50, 75, 100, and 125 mg./Kg., had a definite inhibitory effect on the growth of mammary adenocarcinoma EO 771, but did not completely destroy it. Spontaneous mammary cancers in C3H and in Swiss mice were apparently unaffected by repeated injections of 8-azaguanine. The use of 8-azaguanine in the treatment of mice bearing sarcoma 180, sarcoma T241, Harding-Passey melanoma, Wagner osteogenic sarcoma, or Patterson lymphosarcoma, and of rats bearing Flexner-Jobling carcinoma, sarcoma R39, or Walker carcinosarcoma 256, produced neither an inhibitory nor curative effect upon these tumors.—*K. Sugiura, Sc.D.*

Articles to appear in future issues of *Cancer*

- ALLEN, ARTHUR C.: A reorientation on the histogenesis and clinical significance of cutaneous nevi and melanomas.
- ATKINSON, WILLIAM B., and GUSBERG, SAUL B.: Histochemical studies on abnormal growth of human endometrium.
- BLOOMER, WILLIAM E., and LINDSKOG, GUSTAF E.: The histamine content of neoplastic pulmonary tissues.
- BRUNDSCHWIG, ALEXANDER: Complete excision of pelvic viscera for advanced carcinoma.
- BRUNDSCHWIG, ALEXANDER: Pancreato-total gastrectomy and splenectomy for advanced carcinoma of the stomach.
- BURCHENAL, JOSEPH; LESTER, R. A.; RILEY, J. B., and RHOADS, C. P.: Studies on the chemotherapy of leukemia. I. Effect of certain nitrogen mustards and carbamates on transmitted mouse leukemia.
- FOOTE, FRANK W., JR., and STEWART, FRED W.: A study of the anatomical distribution of intraepithelial epidermoid carcinomas of the cervix.
- FORAKER, ALVAN G.: Gland-like elements in a peripheral neurosarcoma.
- HEIDELBERGER, CHARLES, and JONES, HARDIN B.: Distribution of radioactivity in the mouse following administration of dibenzanthracene labeled in the 9 and 10 positions with carbon 14.
- HEIDELBERGER, CHARLES; KIRK, MARTHA R., and PERKINS, MARION S.: Metabolic degradation in the mouse of dibenzanthracene labeled in the 9 and 10 positions with carbon 14.
- LEVIN, LOUIS: On the possible relationship between adrenocortical function and the leukemic state.
- LEVIN, MORTON L.: Some epidemiological features of cancer.
- LIEBOW, AVERILL A.; LINDSKOG, GUSTAF E., and BLOOMER, WILLIAM E.: Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung.
- LINDSKOG, GUSTAF E., and BLOOMER, W. E.: Bronchogenic carcinoma. A comparison of two consecutive series of one hundred cases each.
- MCCUTCHEON, MORTON; COMAN, DALE REX, and MOORE, FONTAINE B.: Studies on invasiveness of cancer: adhesiveness of malignant cells in various human adenocarcinomas.
- McKAY, DONALD G.; WARE, PAUL F.; ATWOOD, DOUGLAS A., and HARKEN, DWIGHT E.: The diagnosis of bronchogenic carcinoma by smears of bronchoscopic aspirations.
- MCNEER, GORDON, and JAMES, ARTHUR: Resection of stomach and adjacent organs in continuity for advanced cancer.
- MURRAY, MARGARET R., and STOUT, ARTHUR PURDY: A sympathetic ganglioneuroma cultivated in vitro.
- PIERCE, VIRGINIA K., and SLAUGHTER, DANIEL P.: The association of breast and pelvic disease.
- SACHS, ERIC; LARSEN, REUBEN L., and IVY, A. C.: Report on the Illinois Cancer Bulletin.
- SAPHIR, OTTO, and AMROMIN, GEORGE D.: Obscure axillary lymph-node metastasis in carcinoma of the breast.
- SAUER, HANS R.; MACMANUS, JOSEPH E., and BLICK, MICHAEL S.: Primary malignant neoplasms of the vesicovaginal septum.
- SHERMAN, ROBERT S., and PEARSON, T. ARTHUR: The roentgenographic appearance of renal cancer metastasis in bone.
- SPITZ, SOPHIE: The histological effects of nitrogen mustards on human tumors and tissues.
- SUNDERLAND, D. A., and BINKLEY, GEORGE E.: Papillary adenomas of the large intestine.
- TAYLOR, SAMUEL G.; SLAUGHTER, DANIEL P.; SMEJKAL, WALTER; FOWLER, EDSON, and PRESTON, FREDERICK W.: The effect of sex hormones on advanced carcinoma of the breast.
- WINTROBE, MAXWELL M., and HUGULEY, CHARLES M.: Nitrogen-mustard therapy for Hodgkin's disease, lymphosarcoma, the leukemias, and other disorders.